

Europäisches Patentamt
European Patent Office
Office européen des brevets



(11)

EP 0 837 052 B1

(12)

EUROPEAN PATENT SPECIFICATION

(45) Date of publication and mention
of the grant of the patent:
23.08.2006 Bulletin 2006/34

(21) Application number: **96918841.6**

(22) Date of filing: **19.06.1996**

(51) Int Cl.:

<i>C07C 233/52</i> ^(2006.01)	<i>C07C 233/84</i> ^(2006.01)
<i>C07C 271/24</i> ^(2006.01)	<i>C07C 311/06</i> ^(2006.01)
<i>C07C 311/11</i> ^(2006.01)	<i>C07C 311/19</i> ^(2006.01)
<i>C07D 493/08</i> ^(2006.01)	<i>C07D 495/08</i> ^(2006.01)
<i>A61K 31/16</i> ^(2006.01)	<i>C07D 333/24</i> ^(2006.01)
<i>C07D 333/34</i> ^(2006.01)	

(86) International application number:
PCT/JP1996/001685

(87) International publication number:
WO 1997/000853 (09.01.1997 Gazette 1997/03)

(54) **BICYCLIC AMINO DERIVATIVES AND PGD 2 ANTAGONIST CONTAINING THE SAME**
BIZYKLISCHE AMINODERIVATE UND ENTHALTENDE PGD2-ANTAGONISTEN
DERIVES AMINO BICYCLIQUES ET ANTAGONISTE DE PGD 2 CONTENANT CES DERIVES

(84) Designated Contracting States:
**AT BE CH DE DK ES FI FR GB GR IE IT LI LU MC
NL PT SE**
Designated Extension States:
AL LT LV SI

(30) Priority: **21.06.1995 JP 15457595**

(43) Date of publication of application:
22.04.1998 Bulletin 1998/17

(73) Proprietor: **SHIONOGI & CO., LTD.**
Osaka-shi,
Osaka 541-0045 (JP)

(72) Inventors:

- **OHTANI, Mitsuaki**
Nara 630 (JP)
- **ARIMURA, Akinori**
Osaka-shi
Osaka 558 (JP)
- **TSURI, Tatsuo**
Kobe-shi
Hyogo 651-11 (JP)
- **KISHINO, Junji**
Hyogo 654-01 (JP)
- **HONMA, Tsunetoshi**
Nara 630-02 (JP)

(74) Representative: **Hayes, Adrian Chetwynd et al**
Boult Wade Tennant,
Verulam Gardens
70 Gray's Inn Road
London WC1X 8BT (GB)

(56) References cited:

JP-A- 2 180 862	JP-A- 6 279 395
JP-A- 60 178 876	JP-A- 63 139 161

- **HANASAKI, KOHJI ET AL:** "Phorbol ester-induced expression of the common, low-affinity binding site for primary prostanoids in vascular smooth muscle cells" **J. BIOL. CHEM.** (1990), 265 (9), 4871-5, XP002180585
- **HANASAKI, KOHJI ET AL:** "Characterization of platelet thromboxane A2/prostaglandin H2 receptor by a novel thromboxane receptor antagonist, [3H]S-145" **BIOCHEM. PHARMACOL.** (1989), 38(12), 2007-17, XP002180587
- **ARIMURA ET AL:** 'Antiasthmatic Activity of a Novel Thromboxane A2 Antagonist, S-1452, In Guinea Pigs' **INT. ARCH. ALLERGY IMMUNOL.** vol. 98, 1992, pages 239 - 246, XP002916327
- **SENO K.; HAGISHITA S.:** 'Thromboxane A2 Receptor Antagonists. III. Synthesis and Pharmacological Activity of 6,6-Dimethylbicyclo [3.1.1]heptane Derivatives with a substituted Sulfonylamino Group C-2' **CHEM. PHARM. BULL.** vol. 37, no. 6, 1989, pages 1524 - 1533, XP002058537

Note: Within nine months from the publication of the mention of the grant of the European patent, any person may give notice to the European Patent Office of opposition to the European patent granted. Notice of opposition shall be filed in a written reasoned statement. It shall not be deemed to have been filed until the opposition fee has been paid. (Art. 99(1) European Patent Convention).

EP 0 837 052 B1

- GILES H. ET AL: 'The biology and Pharmacology of PGD₂.' PROSTAGLANDINS vol. 35, 1988, pages 277 - 300

Description

FIELD OF THE INVENTION

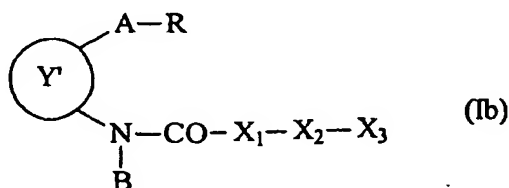
- 5 [0001] The present invention relates to bicyclic amino derivatives and prostaglandin D₂ (hereinafter, referred to as PGD₂) antagonist containing them.

BACKGROUND OF THE INVENTION

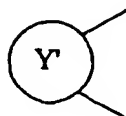
- 10 [0002] Some bicyclic amino derivatives are known to be useful as thromboxane A₂ (TXA₂) antagonists (Japanese Patent Publication No. JP63-139161). However, Japanese Patent Publication No. JP63-139161 only describes the compounds as useful as TXA₂ antagonists, and does not suggest usefulness thereof as PGD₂ antagonists.
- [0003] Namely, TXA₂ is known to have activities such as action against platelet agglutination, thrombogenesis, etc. The TXA₂ antagonist has therefore been considered to be useful as an anti-thrombotic agent, and also in the treatment
- 15 of myocardial infarction or asthma by antagonizing against TXA₂.
- [0004] EP-A-608847 discloses carbocyclic sulfonamides as agonists or antagonists of PGEZ.
- [0005] EP-A-312906 discloses sulfonamide derivatives, which can be used as TXA₂ antagonists.
- [0006] EP-A-0226346 discloses bicyclic sulfonamide derivatives, which can be used as antithrombotic, anti-vasoconstricting and anti-bronchoconstricting drugs.
- 20 [0007] EP-A-0150709 discloses 7-oxabicycloheptane prostaglandin analogs as cardiovascular agents, which are useful in the treatment of thrombolytic disease.
- [0008] EP-A-0290285 discloses bicyclic sulfonamide derivatives and their use in the treatment of diseases such as angina pectoris, myocardial infarction and cerebral infarction.
- [0009] A TXA₂ receptor antagonist, "S-1452", is disclosed in Int. Arc. Allergy Immunol. (1992) 98, 239-246, Arimura et al., "Antiasthmatic Activity of a Novel Thromboxane A₂ Antagonist, S-1452, in Guinea Pigs" (XP 00 291 6327) .
- 25 [0010] On the other hand, the PGD₂ antagonist of the present invention is useful in the improvement of conditions due to excessive production of PGD₂. Specifically, it is useful as a drug for treating diseases in which mast cell dysfunction is involved, for example, systemic mastocytosis and disorder of systemic mast cell activation, and also tracheal contraction, asthma, allergic rhinitis, allergic conjunctivitis, urticaria, injury due to ischemic reperfusion, and inflammation.
- 30 [0011] As is apparent from the above, the TXA₂ antagonist and the PGD₂ antagonist are completely different from each other in terms of the active site, mechanism of action, and application, and have quite different characteristics. Accordingly, it has never been expected that any compound could possess these activities simultaneously.
- [0012] PGD₂ is produced through PGG₂ and PGH₂ from arachidonic acid by the action of cyclooxygenase activated by immunological or unimmunological stimulation and is the major prostanoid that is produced and released from mast
- 35 cells. PGD₂ has various potent physiological and pathological activities. For example, PGD₂ can cause strong tracheal contraction, which leads to bronchial asthma, and, in a systemic allergic state, it can dilate the peripheral vessels, which leads to an anaphylactic shock. Especially, much attention has been paid to the idea that PGD₂ is one of the causal substances responsible for the onset of nasal occlusion in the allergic rhinitis. Therefore, it has been proposed to develop an inhibitor against the biosynthesis of PGD₂ or an antagonist of PGD₂ receptor as a drug for the reduction of nasal occlusion. However, the inhibitor of PGD₂ biosynthesis possibly affects greatly the synthesis of prostaglandins in other
- 40 organisms, and therefore, it is desirable to develop an antagonist (blocker) specific to PGD₂ receptor.

DISCLOSURE OF THE INVENTION

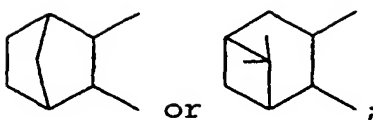
- 45 [0013] The present inventors have studied intensively to develop PGD₂ receptor antagonists (blockers) specific to PGD₂ receptor, and found that compounds of the formula (Ib) below or its salt possess a potent activity as PGD₂ receptor antagonists and are chemically and biochemically stable.
- [0014] Accordingly, the present invention provides a PGD₂ antagonist which comprises a compound of the formula (Ib):



5



10



20

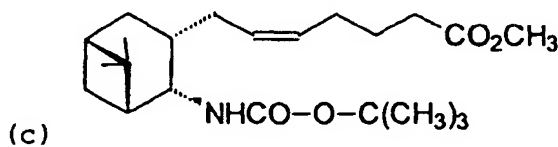
25

30

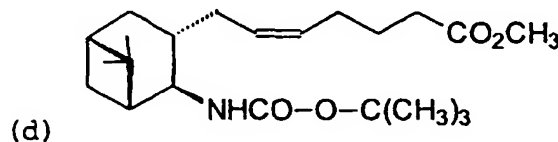
35

40

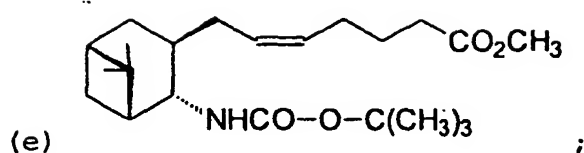
45



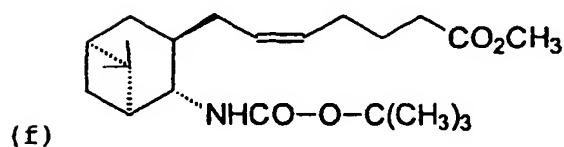
50



55

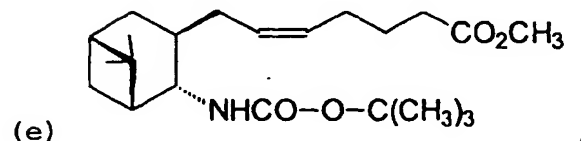
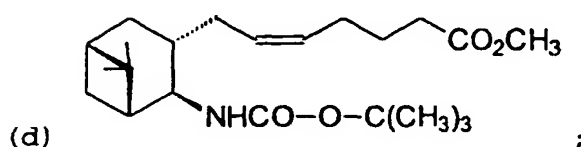
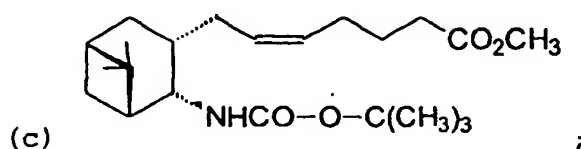


and

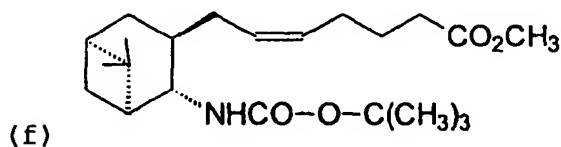


are excluded.

[0015] The compounds of the formulae:



and



45

are excluded from the scope of claim 1 of this application/patent by way of disclaimers, which were introduced into the specification after filing the application. One or more of these compounds appears in each of EP-A-226346, EP-A-290285 and Chem. Pharm. Bull. 37(6), 1524-1533, K. Seno, S. Hagishita, "Thromboxane A2 Receptor Antagonists III. Synthesis and Pharmacological Activity of 6,6-Dimethylbicyclo[3.1.1]heptane Derivatives with a Substituted Sulfonylami-

50

no Group C-2," XP2058537. These compounds have been disclaimed as accidental anticipations, in accordance with the Decisions G1/03 and G2/03.

[0016] Examples of more preferred compounds include those of the formula (Ib) wherein R is COOR₁ (R₁ is as defined above) or a salt or hydrate thereof.

[0017] Similarly, examples of the compounds of the present invention include those of the formula (Ib) wherein X₁ is a phenylene or thiophenediyl, X₂ is a single bond, -N=N-, -CH=CH-, ethynylene, -O-, -S-, -CO-, -CON(R₅₅) - (R₅₅ is as defined above), -N(R₅₁)CO- (R₅₁ is as defined above) and X₃ is phenyl, or a salt or hydrate thereof.

[0018] Examples of more preferred embodiments include those wherein B is hydrogen, both X₁ and X₂ are a single bond, X₃ is thienyl, thiazolyl, thiadiazolyl, isothiazolyl, pyrrolyl, pyridyl, benzofuryl, benzimidazolyl, benzothienyl, dibenzofuryl, dibenzothienyl, quinolyl or indolyl or a salt or hydrate thereof. Similarly, examples include those wherein X₁ is phenylene, thiophenediyl, indolediyl or oxazolediyl, X₂ is a single bond, -N=N-, ethynylene, -S- or -O-, and X₃ is aryl or heterocyclic group, or a salt or hydrate thereof.

[0019] The compounds of the general formula (Ib) are novel compounds synthesized by the present inventors.

[0020] The terms used throughout the present specification are as defined below.

[0021] The term "alkylene" means C₁-C₉ straight or branched chain alkylene, for example, methylene, methylmethylene, dimethylmethylene, methylethylmethylene, ethylene, trimethylene, tetramethylene, pentamethylene, hexamethylene, heptamethylene, octamethylene, nonamethylene, or the like. The alkylene above can be intervened by a hetero atom(s) (oxygen, sulfur, nitrogen atom, or the like) or phenylene (e.g., 1,4-phenylene, 1,3-phenylene, 1,2-phenylene, or the like), contain an oxo group, and/or have one or more double- or triple-bonds at any positions on the chain. Examples include -(CH₂)₂-O-CH₂-, -(CH₂)₂-O-(CH₂)₂-, -(CH₂)₂-O-(CH₂)₃-, -(CH₂)₂-O-(CH₂)₄-, -(CH₂)₂-O-(CH₂)₅-, -(CH₂)₂-O-(CH₂)₆-, -(CH₂)₂-S-(CH₂)₂-, -(CH₂)₃-S-(CH₂)₂-, -CH₂-S-CH₂-, -CH₂-S-(CH₂)₄-, -CH₂-N(CH₃)-CH₂-, -CH₂-NH-(CH₂)₂-, -(CH₂)₂-N(CH₂CH₃)-(CH₂)₃-, -(CH₂)₂-1,4-phenylene-CH₂-, -(CH₂)₂-O-1,3-phenylene-CH₂-, -(CH₂)₂-O-1,2-phenylene-CH₂-, -(CH₂)₂-O-1,4-phenylene-CH₂-, -CH=CH-S-CH₂-1,4-phenylene-CH₂-, -CH=CH-S-1,3-phenylene-(CH₂)₂-, 2-oxopropylene, 3-oxopentylene, 5-oxohexylene, vinylene, 1-propenylene, 2-propenylene, 1-butenylene, 2-butenylene, 3-butenylene, 1,2-butadienylene, 1,3-butadienylene, 1-pentenylene, 2-pentenylene, 3-pentenylene, 4-pentenylene, 1,2-pentadienylene, 1,3-pentadienylene, 1,4-pentadienylene, 2,3-pentadienylene, 2,4-pentadienylene, 1-hexenylenylene, 2-hexenylenylene, 3-hexenylenylene, 4-hexenylenylene, 5-hexenylenylene, 1,2-hexadienylene, 1,3-hexadienylene, 1,4-hexadienylene, 1,5-hexadienylene, 2,3-hexadienylene, 2,4-hexadienylene, 2,5-hexadienylene, 3,4-hexadienylene, 3,5-hexadienylene, 4,5-hexadienylene, 1,1-dimethyl-4-hexenylenylene, 1-heptenylenylene, 2-heptenylenylene, 3-heptenylenylene, 4-heptenylenylene, 5-heptenylenylene, 2,2-dimethyl-5-heptenylenylene, 6-heptenylenylene, 1,2-heptadienylene, 1,3-heptadienylene, 1,4-heptadienylene, 1,5-heptadienylene, 1,6-heptadienylene, 2,3-heptadienylene, 2,4-heptadienylene, 2,5-heptadienylene, 2,6-heptadienylene, 3,4-heptadienylene, 3,5-heptadienylene, 3,6-heptadienylene, 4,5-heptadienylene, 4,6-heptadienylene or 5,6-heptadienylene, 1-propynylene, 3-butylenylene, 2-pentylenylene, 5-hexynylene, 6-heptynylenylene, -(CH₂)-CH=CH-O-(CH₂)₂-, -CH₂-S-(CH₂)₃-, -CH₂-cis-CH=CH-1,2-phenylene-CH₂-, -CH=CH-1,4-phenylene-(CH₂)₂-, -4-oxo-4,5-hexenylenylene-, and the like.

[0022] The term "alkyl" means C₁-C₂₀ straight or branched chain alkyl, for example, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, n-pentyl, i-pentyl, neopentyl, t-pentyl, hexyl, heptyl, octyl, nonyl, decyl, undecyl, dodecyl, tridecyl, tetradecyl, pentadecyl, hexadecyl, heptadecyl, octadecyl, nonadecyl, icosyl, and the like.

[0023] The term "aryl" means C₆-C₁₄ monocyclic or condensed ring, for example, phenyl, naphthyl (e.g., 1-naphthyl, 2-naphthyl), anthryl (e.g., 1-anthryl, 2-anthryl, 9-anthryl), phenanthryl (e.g., 2-phenanthryl, 3-phenanthryl, 9-phenanthryl), fluorenyl (e.g., 2-fluorenyl), and the like. Phenyl is especially preferred.

[0024] The term "aralkyl" means a group formed by substituting an alkyl as defined above with an aryl above at any substitutable positions on the alkyl. Examples include benzyl, phenethyl, phenylpropyl (e.g., 3-phenylpropyl), naphthylmethyl (e.g., α-naphthylmethyl), anthrylmethyl (e.g., 9-anthrylmethyl), phenanthrylmethyl (e.g., 3-phenanthrylmethyl), and the like.

[0025] The term "acyl" means C₁-C₉ acyl derived from aliphatic carboxylic acid, for example, formyl, acetyl, propionyl, butyryl, valeryl, and the like.

[0026] The term "alkylsulfonyl" means a group formed by substituting a sulfonyl with an alkyl above, for example, methylsulfonyl, ethylsulfonyl, propylsulfonyl, and the like.

[0027] The term "alkenyl" is C₂-C₂₀ straight or branched chain alkenyl, which corresponds to an alkyl above containing one or more double bonds. Examples include vinyl, 1-propenyl, 2-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 1,2-butadienyl, 1-pentenyl, 1,2-pentadienyl, 2-hexenyl, 1,2-hexadienyl, 3-heptenyl, 1,5-heptadienyl, and the like. The term "alkynyl" is C₂-C₂₀ straight or branched chain, alkynyl, which corresponds to an alkyl above containing one or more triple bonds. Examples include ethynyl, 1-propynyl, 2-propynyl, 1-butylenyl, 2-butylenyl, 3-butylenyl, and the like.

[0028] The term "heterocyclic group" means 5-7 membered cyclic group containing one or more hetero atoms selected independently from the group consisting of oxygen, sulfur and/or nitrogen atom on the ring, and is optionally condensed with a carbon ring or other heterocyclic group at any substitutable positions. Examples include pyrrolyl (e.g., 1-pyrrolyl, 3-pyrrolyl), indolyl (e.g., 2-indolyl, 3-indolyl, 6-indolyl), carbazoyl (e.g., 2-carbazoyl, 3-carbazoyl), imidazolyl (e.g., 1-imidazolyl, 4-imidazolyl), pyrazolyl (e.g., 1-pyrazolyl, 3-pyrazolyl), benzimidazolyl (e.g., 2-benzimidazolyl, 5-benzimidazolyl), indazolyl (e.g., 3-indazolyl), indolizynyl (e.g., 6-indolizynyl), pyridyl (e.g., 2-pyridyl, 3-pyridyl, 4-pyridyl), quinolyl

(e.g., 8-quinolyl), isoquinolyl (e.g., 3-isoquinolyl), acridyl (e.g., 1-acridyl), phenanthrydyl (e.g., 2-phenanthrydyl, 3-phenanthrydyl), pyridazinyl (e.g., 3-gydidazinyl), pyrimidinyl (e.g., 4-pyrimidinyl), pyrazinyl (e.g., 2-pyrazinyl), cinnolyl (e.g., 3-cinnolyl), phthaladyl (e.g., 5-phthaladyl), quinazolinyl (e.g., 2-quinazolinyl), isoxazolyl (e.g., 3-isoxazolyl, 4-isoxazolyl), benzisoxazolyl (e.g., 1,2-benzisoxazol-4-yl, 2,1-benzisoxazol-3-yl), oxazolyl (e.g., 2-oxazolyl, 4-oxazolyl, 5-oxazolyl), benzoxazolyl (e.g., 2-benzoxazolyl), benzoxadiazolyl (e.g., 4-benzoxadiazolyl), isothiazolyl (e.g., 3-isothiazolyl, 4-isothiazolyl) benzisothiazolyl (e.g., 1,2-benzisothiazol-3-yl, 2,1-benzisothiazol-5-yl), thiazolyl (e.g., 2-thiazolyl), benzothiazolyl (e.g., 2-benzothiazolyl), thiadiazolyl (e.g., 1,2,3-thiadiazol-4-yl), oxadiazolyl (e.g., 1,3,4-oxadiazol-2-yl), dihydroxadiazolyl (e.g., 4,5-dihydro-1,2,4-oxadiazol-3-yl), furyl (e.g., 2-furyl, 3-furyl), benzofuryl (e.g., 3-benzofuryl), isobenzofuryl (e.g., 1-isobenzofuryl), thienyl (e.g., 2-thienyl, 3-thienyl), benzothienyl (1-benzothienyl, 2-benzothienyl, 3-benzothienyl), tetrazolyl (e.g., 5-tetrazolyl), benzodioxolyl (e.g., 1,3-benzodioxol-5-yl), dibenzofuryl (e.g., 2-dibenzofuryl, 3-dibenzofuryl), dibenzoxepinyl (e.g., dibenz[b,f]oxepin-2-yl), dihydrodibenzoxepinyl (e.g., dihydrodibenz[b,f]oxepin-2-yl), chromenyl (e.g., 2H-chromen-3-yl, 4H-chromen-2-yl), dibenzothiepinyl (e.g., dibenzo[b,f]thiepin-3-yl, dihydrodibenzo[b,f]thiepin-3-yl), morpholinyl (e.g., 1,4-morpholin-4-yl), phenothiadyl (2-phenothiadyl), cyclopentathienyl (e.g., cyclopenta[b]thiophen-3-yl), cyclohexathienyl (e.g., cyclohexa[b]thiophen-3-yl), cycloheptathienyl (e.g., cyclohepta[b]thiophen-3-yl), dibenzothienyl (e.g., 2-dibenzothienyl), dibenzopyranyl (e.g., 2-dibenzopyranyl), dibenzo-p-dioxyl (e.g., 2-dibenzo-p-dioxyl), and the like.

[0029] The term "cycloalkyl" means C₃ - C₈ cyclic alkyl, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and the like.

[0030] The term "cycloalkenyl" means C₃ - C₈ cyclic alkenyl, for example, cyclopropenyl (e.g., 1-cyclopropenyl), cyclobutenyl (e.g., 2-cyclobuten-1-yl), cyclopentenyl (1-cyclopenten-1-yl), cyclohexenyl (1-cyclohexen-1-yl), and the like.

[0031] The term "alkoxy" means C₁ - C₆ alkoxy, for example, methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, and the like.

[0032] Examples of the substituted amino in the definition of "substituted- or un-substituted-amino" include mono- or disubstituted amino such as methylamino, ethylamino, dimethylamino, cyclohexylamino, phenylamino, diphenylamino, or cyclic amino such as piperidino, piperadino or morpholino.

[0033] The term "acyloxy" means an acyloxy derived from the "acyl" above, for example, acetyloxy, propionyloxy, butyryloxy, valeryloxy, and the like.

[0034] The term "halogen" means fluorine, chlorine, bromine and iodine.

[0035] The term "alkoxycarbonyl" means an alkoxycarbonyl group derived from the "alkoxy" above, for example, methoxycarbonyl, ethoxycarbonyl, phenyloxycarbonyl, and the like.

[0036] The term "aralkyloxycarbonyl" means an aralkyloxycarbonyl group derived from the "aralkyl" above, for example, benzyloxycarbonyl, phenethyloxycarbonyl, and the like.

[0037] The term "aryloxycarbonyl" means an aryloxycarbonyl group derived from the "aryl" above, for example, phenyloxycarbonyl, naphthyloxycarbonyl, and the like.

[0038] The term "alkenyloxy" means an alkenyloxy group derived from the "alkenyl" above, for example, vinyloxy, 1-propenyloxy, 2-butenyloxy, and the like.

[0039] The term "hydroxyalkyl" means a hydroxyalkyl group derived from the "alkyl" above, for example, hydroxymethyl, hydroxyethyl, hydroxypropyl, and the like.

[0040] The term "alkylthio" means an alkylthio group derived from the "alkyl" above, for example, methylthio, ethylthio, propylthio, and the like.

[0041] The term "alkylenedioxy" means C₁ - C₃ alkylenedioxy, for example, methylenedioxy, ethylenedioxy, propylenedioxy, and the like.

[0042] In the case of "phenylene", "naphthylene", "thiophenediyl", "indolediyl", "oxazolediyl", "oxadiazolediyl" and "tetrazolediyl", the said group can bind to the neighboring groups at any two substitutable sites.

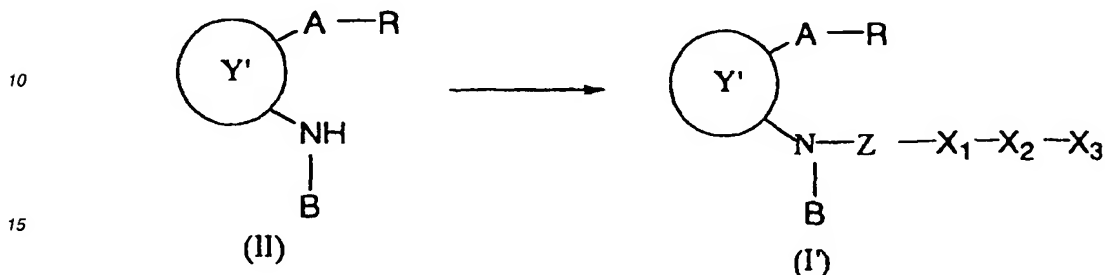
[0043] In the definitions above, when a substituent(s) is cyclic, it may be substituted by one to three substituents selected from nitro, alkoxy, sulfamoyl, substituted- or un-substituted-amino, acyl, acyloxy, hydroxy, halogen, alkyl, alkenyl, carboxy, alkoxycarbonyl, aralkoxycarbonyl, aryloxycarbonyl, mesyloxy, cyano, alkenyloxy, hydroxyalkyl, trifluoromethyl, alkylthio, -N=PPh₃, oxo, thioxo, hydroxyimino, alkoxyimino, phenyl and alkylenedioxy. The substituent(s) may bind to any substitutable positions on the ring.

[0044] Examples of salts of the compound (Ib) include those formed with an alkali metal (e.g., lithium, sodium or potassium), an alkaline earth metal (e.g., calcium), an organic base (e.g., tromethamine, trimethylamine, triethylamine, 2-aminobutane, t-butylamine, diisopropylethylamine, n-butylmethylamine, cyclohexylamine, dicyclohexylamine, N-isopropylcyclohexylamine, furfurylamine, benzylamine, methylbenzylamine, dibenzylamine, N,N-dimethylbenzylamine, 2-chlorobenzylamine, 4-methoxybenzylamine, 1-naphthylmethanemethylamine, diphenylbenzylamine, triphenylamine, 1-naphthylamine, 1-aminoanthracene, 2-aminoanthracene, dehydroabiethylamine, N-methylmorpholine or pyridine), an amino acid (e.g., lysine, or arginine), and the like.

[0045] The term "hydrate" means a hydrate of the compound of the formula (Ib) or its salt. Examples include mono- and dihydrates.

[0046] The present compounds are shown by the formula (Ib) and are inclusive of the form of any types of stereoisomers (e.g., diastereomer, epimer, enantiomer) and racemic compounds.

[0047] Compounds of the general formula (Ib) can be prepared by reacting an amino compound of the general formula (II) with a reactive derivative of sulfonic acid or carboxylic acid corresponding to the partial structure: $Z-X_1-X_2-X_3$ as shown below.



Wherein A, B, R, X_1 , X_2 , X_3 , Y are as defined above and Z is -CO-. A carboxylic acid corresponding to the said partial structure is a compound of the general formula $X_3-X_2-X_1-\text{COOH}$. Reactive derivative of these carboxylic acids means a corresponding halide (e.g., chloride, bromide, iodide), acid anhydride (e.g., mixed acid anhydride with formic acid or acetic acid), active ester (e.g., succinimide ester), and examples thereof generally include acylating agents used for the acylation of amino group. The carboxylic acid $X_3-X_2-X_1-\text{COOH}$ can be used in the reaction as it is without converting into a reactive derivative, in the presence of a condensing agent (e.g., dicyclohexylcarbodiimide (DCC), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide, N,N'-carbonyldiimidazole) which are used in the condensing reaction between amine and carboxylic acid.

[0048] The reaction can be conducted under the conditions generally used for the acylation of amino groups. For example, in the case of condensation using an acid halide, the reaction is carried out using a solvent such as an ether solvent (e.g., diethylether, tetrahydrofuran, dioxane), benzene solvent (e.g., benzene, toluene, xylene), halogenated hydrocarbon solvent (e.g., dichloromethane, dichloroethane, chloroform), ethyl acetate, dimethylformamide, dimethyl sulfoxide, acetonitrile, or the like, if necessary, in the presence of a base (e.g., organic base such as triethylamine, pyridine, N,N-dimethylaminopyridine, N-methylmorpholine; inorganic base such as sodium hydroxide, potassium hydroxide, potassium carbonate, or the like) under cooling, at room temperature or under heating, preferably at temperature ranging from -20°C to a temperature under cooling, or from room temperature to a refluxing temperature of the reaction system, for several min to several hr, preferably for 0.5 hr to 24 hr, more preferably, for 1 hr to 12 hr.

[0049] The reaction conditions for the reaction between other reactive derivative or a free acid and an amine (II) can be determined in a conventional manner depending on the characteristics of the respective reactive derivative or free acid.

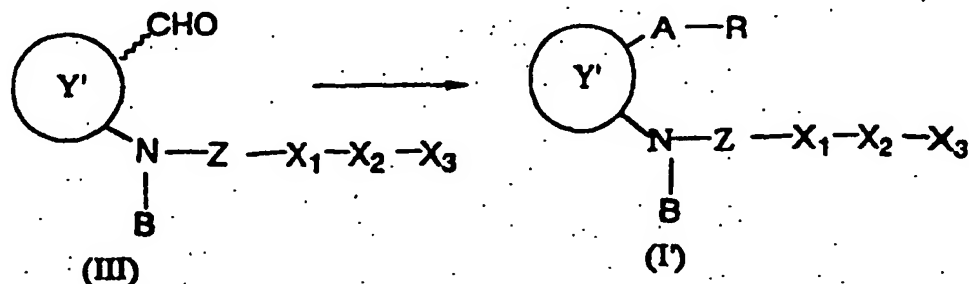
[0050] The reaction product can be purified by conventional purification methods, for example, the extraction with a solvent, chromatography, recrystallization, or the like.

[0051] Specific examples of the compound (II) as a starting material for the present method are as follows. -Examples of 3-amino[2.2.1]bicyclic compound include 7-(3-aminobicyclo[2.2.1]hept-2-yl)-5-heptenoic acid, 7-(3-aminobicyclo[2.2.1]hept-2-yl)-2,2-dimethyl-5-heptenoic acid, 7-(N-methyl-3-aminobicyclo[2.2.1]hept-2-yl)-5-heptenoic acid, 6-(3-aminobicyclo[2.2.1]hept-2-yl)-5-hexenoic acid. Specific examples of 2-amino-6,6-dimethyl[3.1.1]bicyclic compound include 7-(2-amino-6,6-dimethylbicyclo[3.1.1]hept-3-yl)-5-heptenoic acid. In these starting compounds, the heptenoic acid chain may be saturated to form heptanoic acid chain, intervened by a hetero atom(s) or a hetero group(s) such as -O-, -S-, -NH-, or a phenylene(s), or substituted with an oxo group. Examples of such compounds include 7-(3-aminobicyclo[2.2.1]hept-2-yl)heptanoic acid, 4-[2-(2-aminobicyclo[3.1.1]hept-3-yl)ethoxyphenyl]acetic acid, 7-(3-aminobicyclo[2.2.1]hept-2-yl)-6-oxo-heptanoic acid. These starting compounds are either described in the Japanese Patent Publication No. JP 63-139161 or JP 01-52751, or can be prepared according to the method described therein.

[0052] Carboxylic acid $X_3-X_2-X_1-\text{COOH}$ corresponding to the partial structure $Z-X_1-X_2-X_3$ mean a carboxylic acid having substituents corresponding to the X s above. That is, examples include alkane-carboxylic acid, alkene-carboxylic acid, alkyne-carboxylic acid, cycloalkane-carboxylic acid, cycloalkene-carboxylic acid, aryl-carboxylic acid, aralkyloxy-carboxylic acid, heterocyclic-substituted-carboxylic acid, heteroarylalkyl-carboxylic acid, and substituted-amino-carboxylic acid. Each of the carboxylic acids may have a substituent(s) above. These carboxylic acids are commercially available or can be easily synthesized from a known compound(s) in accordance with a known method. Upon reaction, the carboxylic acid can be converted into the corresponding reactive derivative above, if necessary. For example, when an acid halide is needed, the compound is reacted with thionyl halide (e.g., thionyl chloride), phosphorous halide (e.g., phosphorous trichloride, phosphorous pentachloride) or oxalyl halide (e.g., oxalyl chloride) in accordance with a known

method such as those described in the literature (e.g., Shin-Jikken-Kagaku-Koza, vol. 14, pp. 1787 (1978), Synthesis, 852-854 (1986); Shin-Jikken-Kagaku-Koza, vol. 22, pp. 115 (1992)). The other reactive derivatives can also be prepared in accordance with known methods.

[0053] Among the objective compounds (Ib), those wherein the side chain A contains an unsaturated bond, especially a double bond, can also be prepared by reacting an aldehyde derivative of the general formula (III) below with an ylide compound corresponding to the rest of the side chain A-R under the conditions of the Wittig reaction:



wherein A, B, R, X₁, X₂, X₃, Y are as defined above, and Z is -CO-.

[0054] The starting compound (III) can be prepared in accordance with a method described in, for example, Japanese Patent Publication No. JP 02-256650. Further, an ylide compound corresponding to the rest of the side chain A-R can be synthesized by reacting triphenylphosphine with a corresponding halogenated alkanic acid, or an ester derivative, ether derivative or amide derivative thereof in the presence of a base according to a known method.

[0055] Among the objective compounds (Ib), those wherein R is COOH can be converted into a corresponding ester derivative, alcohol derivative, ether derivative, amide derivative, if desired. For example, ester derivatives can be prepared by esterifying a carboxylic acid in a conventional manner. An ester derivative, when reduced, gives an alcohol derivative, and amidated, gives an amide derivative. An ether derivative can be obtained by O-alkylating an alcohol derivative.

[0056] The compound (Ib) of the present invention shows antagonistic effect against PGD₂ in vitro through the binding to PGD₂ receptor, and is useful as a drug for treating diseases in which mast cell dysfunction due to excessive production of PGD₂ is involved. For example, the compound (Ib) is useful as a drug for treating diseases, such as systemic mastocytosis and disorder of systemic mast cell activation, and also tracheal contraction, asthma, allergic rhinitis, allergic conjunctivitis, urticaria, injury due to ischemic reperfusion, and inflammation. The compound (Ib) shows preventive effect on nasal occlusion in vivo, and therefore is especially useful as a drug for treating that.

[0057] When using a compound (Ib) of the present invention in treatment, it can be formulated into ordinary formulations for oral and parenteral administration. A pharmaceutical composition containing a compound (Ib) of the present invention can be in the form for oral and parenteral administration. Specifically, it can be formulated into formulations for oral administration such as tablets, capsules, granules, powders, syrup, and the like; those for parenteral administration such as injectable solutions or suspensions for intravenous, intramuscular or subcutaneous injection, inhalant, eye drops, nasal drops, suppositories, or percutaneous formulations such as ointments.

[0058] In preparing the formulations, carriers, excipients, solvents, and bases known to one ordinary skilled in the art may be used. In case of tablets, they are prepared by compressing or formulating an active ingredient together with auxiliary components. Examples of usable auxiliary components include pharmaceutically acceptable excipients such as binders (e.g., cornstarch), fillers (e.g., lactose, microcrystalline cellulose), disintegrants (e.g., starch sodium glycolate) or lubricants (e.g., magnesium stearate). Tablets may be coated appropriately. In the case of liquid formulations such as syrups, solutions, or suspensions, they may contain suspending agents (e.g., methyl cellulose), emulsifiers (e.g., lecithin), preservatives, and the like. In the case of injectable formulations, it may be in the form of solution or suspension, or oily or aqueous emulsion, which may contain suspension-stabilizing agent or dispensing agent, and the like. In the case of an inhalant, it is formulated into a liquid formulation applicable to an inhaler. In the case of eye drops, it is formulated into a solution or a suspension. Especially, in the case of nasal drug for treating nasal occlusion, it can be used as a solution or suspension prepared by a conventional formulating method, or as a powder formulated using a powdering agent (e.g., hydroxypropyl cellulose, carbopole), which are administered into the nasal cavity. Alternatively, it can be used as an aerosol after filling into a special container together with a solvent of low boiling point.

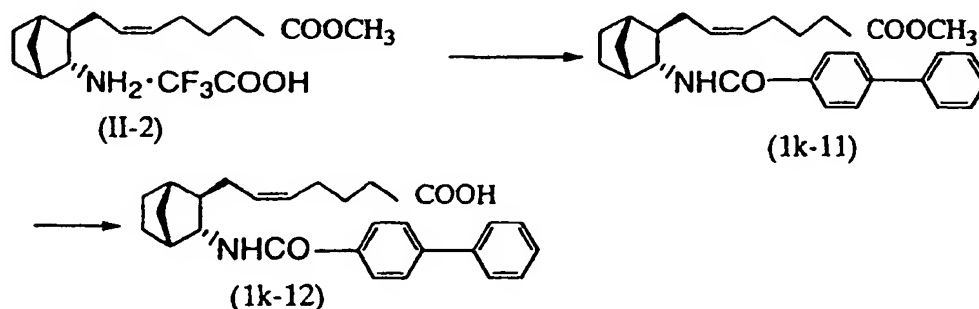
[0059] Although an appropriate dosage of the compound (Ib) varies depending on the administration route, age, body weight, sex, or condition of the patient, and the kind of drug(s) used together, if any, and should be determined by the physician in the end, in the case of oral administration, the daily dosage can generally be between about 0.01 - 100 mg, preferably about 0.01 - 10 mg, more preferably about 0.1 - 10 mg, per kg body weight. In the case of parenteral

administration, the daily dosage can generally be between about 0.001 - 100 mg, preferably about 0.001 - 1 mg, more preferably about 0.01 - 1 mg, per kg body weight. The daily dosage can be administered in 1 - 4 divisions.

[0060] The following Examples are provided to further illustrate the present invention and are not to be construed as limiting the scope thereof.

Example 1

[0061]



[0062] Methyl (Z)-7-[(1S,2R,3R,4R)-3-aminobicyclo[2.2.1]hept-2-yl]-5-heptenoate trifluoroacetate (II-2) (232 mg, 0.636 mmol), which was prepared by the method described in Reference Example 4 of the Japanese Patent Publication No. JP 63-139161, was dissolved in methylene chloride (5 ml). To the solution were added triethylamine (0.279 ml, 2.00 mmol) and 4-biphenylcarbonyl chloride under ice-cooling and stirred for 7 hr at the same temperature. The reaction mixture was purified by column chromatography on silica gel (ethyl acetate/n-hexane (1:4)) to yield methyl (Z)-7-[(1S,2R,3R,4R)-3-(4-biphenyl)carbonylamino-bicyclo[2.2.1]hept-2-yl]-5-heptenoate (1k-11) (221 mg, 0.512 mmol). The compound (1k-11) (190 mg, 0.440 mmol) was dissolved in methanol (6ml). To the solution was added 1 N KOH (1.10 ml, 1.10 mmol) under ice-cooling and stirred for 15 hr at room temperature. The reaction mixture was concentrated in vacuo. The residue, after the addition of water (20 ml) and 1 N HCl (2 ml), was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous sodium sulfate and concentrated. The residue was purified by column chromatography on silica gel (ethyl acetate/hexane (1:1) containing 0.3 % acetic acid) to yield (Z)-7-[(1S,2R,3R,4R)-3-(4-biphenyl)carbonylamino-bicyclo[2.2.1]hept-2-yl]-5-heptenoic acid (1k-12) (172 mg, 0.412 mmol). Yield 94 %.

[0063] The following compounds can also be prepared in the following manner.

[0064] Compounds prepared in accordance with a method described in the Example above are shown in Tables below.

Table 1k

<div style="border: 1px solid black; padding: 10px; display: inline-block;"> </div>		
No.	R ₁	X ₁ -X ₂ -X ₃
1k-1	H	
1k-2	CH ₃	
1k-3	H	

(continued)

No.	R_1	$X_1-X_2-X_3$
1k-4	H	
1k-5	H	
1k-6	H	
1k-7	H	
1k-8	H	
1k-9	H	
1k-10	H	
1k-11	CH_3	
1k-12	H	
1k-13	H	
1k-14	H	
1k-15	H	
1k-16	H	
1k-17	H	
1k-18	H	

(continued)

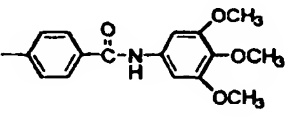
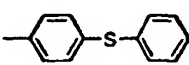
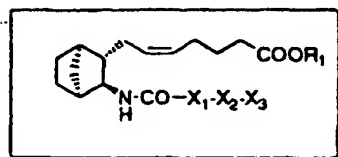
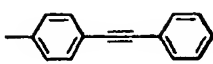
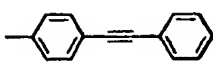
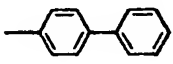
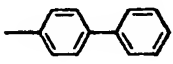
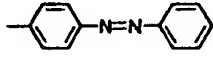
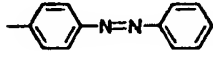
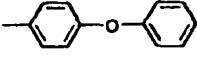
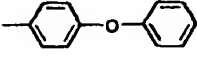
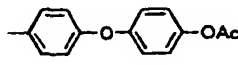
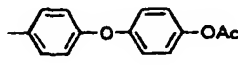
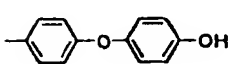
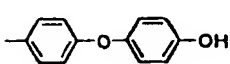
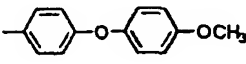
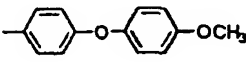
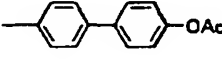
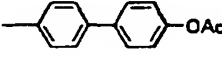
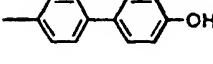
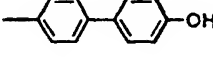
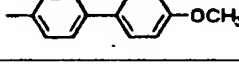
No.	R ₁	X ₁ -X ₂ -X ₃
1k-19	H	
1k-20	H	

Table 1m



No.	R ₁	X ₁ -X ₂ -X ₃
1m-1	CH ₃	
1m-2	H	
1m-3	CH ₃	
1m-4	H	
1m-5	CH ₃	
1m-6	H	
1m-7	CH ₃	
1m-8	H	
1m-9	CH ₃	
1m-10	H	
1m-11	CH ₃	
1m-12	H	
1m-13	CH ₃	
1m-14	H	
1m-15	CH ₃	
1m-16	H	
1m-17	CH ₃	
1m-18	H	
1m-19	CH ₃	

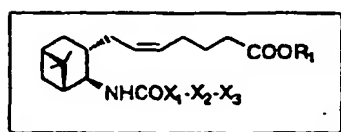
(continued)

No.	R ₁	X ₁ -X ₂ -X ₃
1m-20	H	
5 1m-21	H	
1m-22	H	
10 1m-23	CH ₃	
1m-24	H	
1m-25	CH ₃	
15 1m-26	H	
1m-27	CH ₃	
1m-28	H	
20 1m-29	CH ₃	
1m-30	H	
1m-31	H	
25 1m-32	H	
30 1m-33	H	
1m-34	H	
35 1m-35	H	
40 1m-36	H	
45 1m-37	H	
50 1m-38	H	
55 1m-39	H	

(continued)

No.	R ₁	X ₁ -X ₂ -X ₃
1m-39	H	
1m-40	H	

Table 2a

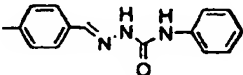
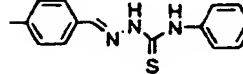
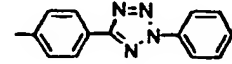
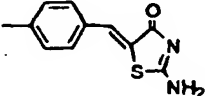
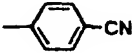
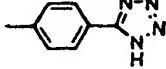
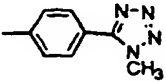
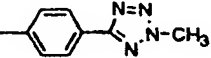
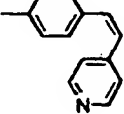
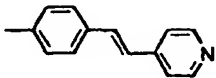
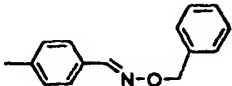
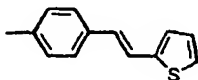


No.	R ₁	X ₁ -X ₂ -X ₃
2a-1	CH ₃	
2a-2	H	
2a-3	CH ₃	
2a-4	H	
2a-5	Na	
2a-6	CH ₃	
2a-7	H	
2a-8	CH ₃	
2a-9	H	
2a-10	CH ₃	
2a-11	H	
2a-12	CH ₃	
2a-13	H	
2a-14	CH ₃	
2a-15	H	

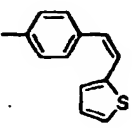
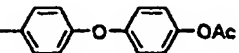
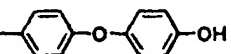
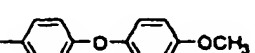
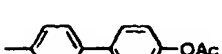
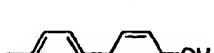




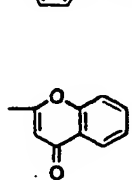



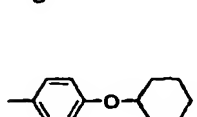
(continued)

	No.	R ₁	X ₁ -X ₂ -X ₃
5	2a-16	CH ₃	
	2a-17	H	
10	2a-18	CH ₃	
	2a-19	H	
15	2a-20	CH ₃	
	2a-21	H	
	2a-22	Na	
	2a-23	CH ₃	
20	2a-24	H	
	2a-25	CH ₃	
	2a-26	H	
25	2a-27	CH ₃	
	2a-28	H	
30	2a-29	CH ₃	
	2a-30	H	
35	2a-31	CH ₃	
	2a-32	CH ₃	
40	2a-33	H	
	2a-34	CH ₃	
	2a-35	H	
45	2a-36	CH ₃	
	2a-37	H	
50	2a-38	CH ₃	
	2a-39	H	
55	2a-40	CH ₃	
	2a-41	H	
	2a-42	CH ₃	
	2a-43	H	


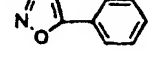
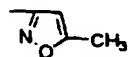
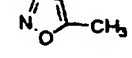
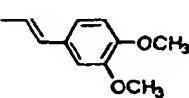
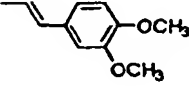
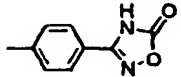
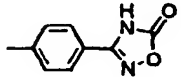
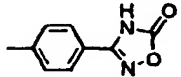
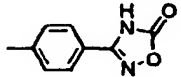
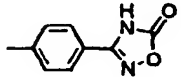
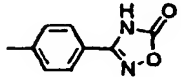
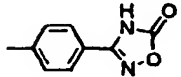
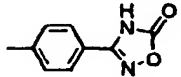
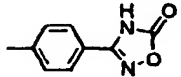
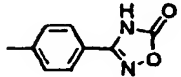
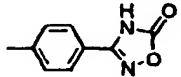
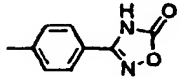
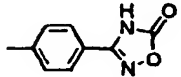
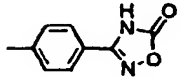
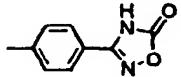
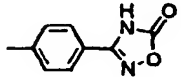
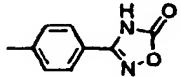
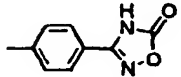
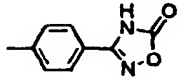
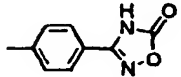
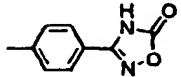
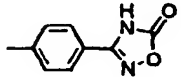
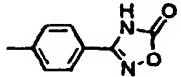
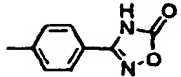
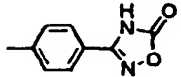
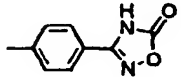
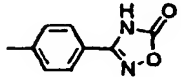
(continued)

No.	R ₁	X ₁ -X ₂ -X ₃
2a-44	CH ₃	
2a-45	H	
2a-46	CH ₃	
2a-47	H	
2a-48	CH ₃	
2a-49	H	
2a-50	CH ₃	
2a-51	H	
2a-52	CH ₃	
2a-53	H	
2a-54	CH ₃	
2a-55	H	
2a-56	CH ₃	
2a-57	H	
2a-58	CH ₃	
2a-59	H	
2a-60	CH ₃	
2a-61	H	
2a-62	CH ₃	
2a-63	H	
2a-64	CH ₃	
2a-65	H	
2a-66	CH ₃	
2a-67	H	

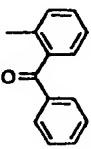
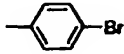
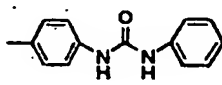
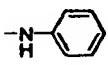
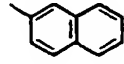
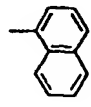
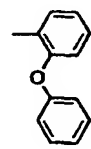
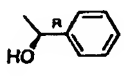
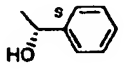
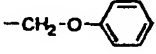
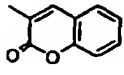
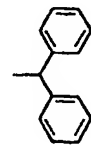
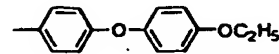
(continued)

	No.	R ₁	X ₁ -X ₂ -X ₃
5	2a-68	CH ₃	
	2a-69	H	
10	2a-70	CH ₃	
	2a-71	H	
	2a-72	CH ₃	
	2a-73	H	
15	2a-74	CH ₃	
	2a-75	H	
20	2a-76	CH ₃	
	2a-77	H	
	2a-78	CH ₃	
	2a-79	H	
25	2a-80	CH ₃	
	2a-81	H	
	2a-82	CH ₃	
	2a-83	H	
30	2a-84	CH ₃	
	2a-85	H	
	2a-86	CH ₃	
35			
	2a-87	H	
40	2a-88	CH ₃	
	2a-89	H	
45	2a-90	CH ₃	
	2a-91	H	
	2a-92	CH ₃	
	2a-93	H	
50	2a-94	CH ₃	
	2a-95	H	
	2a-96	Na	
55	2a-97	Ca ^{1/2}	
	2a-98	CH ₃	
	2a-99	H	

(continued)

	No.	R ₁	X ₁ -X ₂ -X ₃
5	2a-100	CH ₃	
	2a-101	H	
	2a-102	CH ₃	
10	2a-103	H	
	2a-104	CH ₃	
	2a-105	H	
15	2a-106	CH ₃	
	2a-107	H	
	2a-108	CH ₃	
20	2a-109	H	
	2a-110	Na	
	2a-111	CH ₃	
25	2a-112	H	
	2a-113	CH ₃	
	2a-114	H	
30	2a-115	CH ₃	
	2a-116	H	
	2a-117	CH ₃	
35	2a-118	H	
	2a-119	H	
	2a-120	H	
40	2a-121	H	
	2a-122	H	
	2a-123	H	
45	2a-124	H	
	2a-125	H	
	2a-126	H	
50	2a-127	H	
	2a-128	H	
	2a-129	H	
55	2a-130	H	
	2a-131	H	
	2a-132	H	



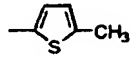
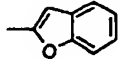
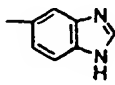
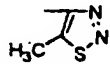

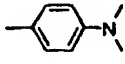
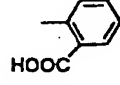
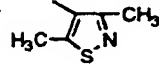
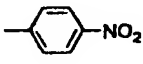



(continued)

	No.	R ₁	X ₁ -X ₂ -X ₃
5	2a-125	H	
10	2a-126	H	
15	2a-127	H	
20	2a-128	H	
25	2a-129	H	
30	2a-130	H	
35	2a-131	H	
40	2a-132	H	
45	2a-133	H	
50	2a-134	H	
55	2a-135	H	
	2a-136	H	
	2a-137	H	

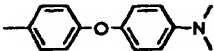
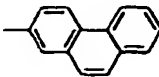
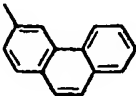
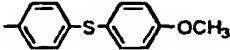
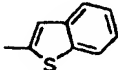
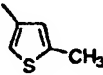
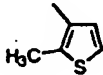


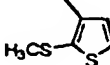

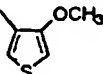
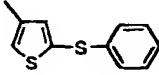
(continued)

No.	R ₁	X ₁ -X ₂ -X ₃
5 2a-138	H	
10 2a-139	H	
15 2a-140	H	
20 2a-141	H	
25 2a-142	H	
30 2a-143	H	
35 2a-144	H	
40 2a-145	H	
45 2a-146	H	
50 2a-147	H	
55 2a-148	H	
2a-149	H	
2a-150	H	
2a-151	H	


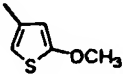
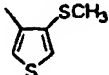
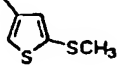
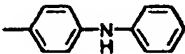
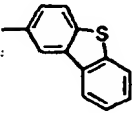
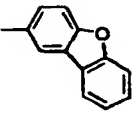
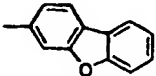
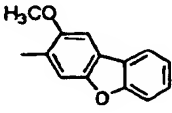



(continued)

No.	R ₁	X ₁ -X ₂ -X ₃
5 2a-152	H	
10 2a-153	H	
2a-154	H	
15 2a-155	H	
20 2a-156	H	
25 2a-157	H	
30 2a-158	H	
35 2a-159	H	
40 2a-160	H	
45 2a-161	H	
50 2a-162	H	
2a-163	H	
55 2a-164	H	
2a-165	H	




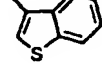
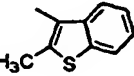
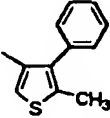
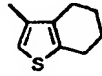
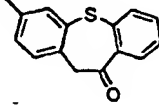
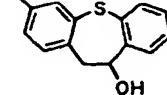
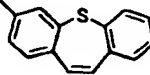
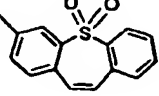
(continued)

No.	R ₁	X ₁ -X ₂ -X ₃
5 2a-166	H	
10 2a-167	H	
15 2a-168	H	
20 2a-169	H	
25 2a-170	H	
30 2a-171	H	
35 2a-172	H	
40 2a-173	H	
45 2a-174	H	
50 2a-175	H	
55 2a-176	H	
2a-177	H	
2a-178	H	

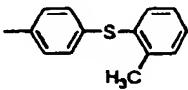

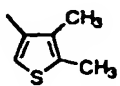
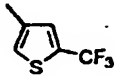
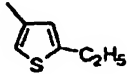
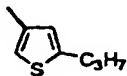
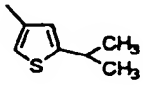
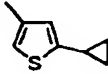
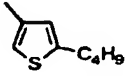
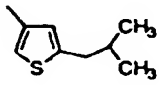
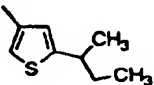
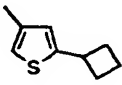
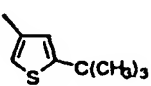
(continued)

No.	R ₁	X ₁ -X ₂ -X ₃
5 2a-179	H	
10 2a-180	H	
15 2a-181	H	
20 2a-182	H	
25 2a-183	H	
30 2a-184	H	
35 2a-185	H	
40 2a-186	H	
45 2a-187	H	
50 2a-188	H	
55 2a-189	H	
2a-190	H	

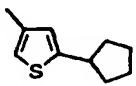
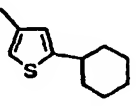
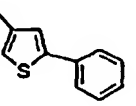
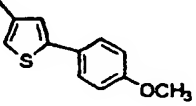
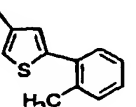
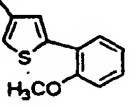
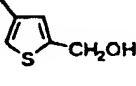
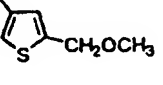
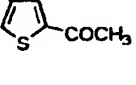
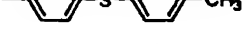

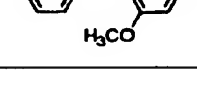
(continued)

No.	R ₁	X ₁ -X ₂ -X ₃
5 2a-191	H	
10 2a-192	H	
15 2a-193	H	
20 2a-194	H	
25 2a-195	H	
30 2a-196	H	
35 2a-197	H	
40 2a-198	H	
45 2a-199	H	
50 2a-200	H	
55 2a-201	H	

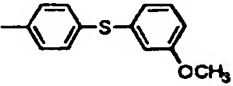
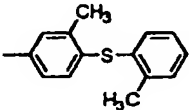
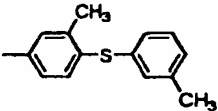
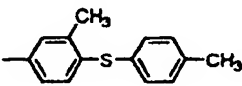
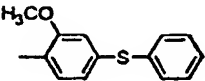
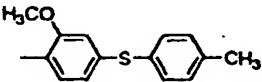
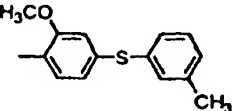
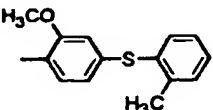
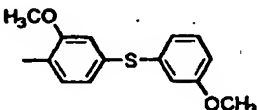
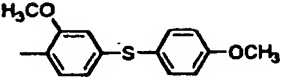
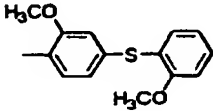
(continued)

No.	R ₁	X ₁ -X ₂ -X ₃
5 2a-202	H	
10 2a-203	H	
2a-204		
15 2a-205		
20 2a-206		
25 2a-207		
30 2a-208		
35 2a-209		
40 2a-210		
45 2a-211		
50 2a-212		
55 2a-213		
2a-214		

(continued)

No.	R ₁	X ₁ -X ₂ -X ₃
5	2a-215	
10	2a-216	
15	2a-217	
20	2a-218	
25	2a-219	
30	2a-220	
35	2a-221	
40	2a-222	
45	2a-223	
50	2a-224	
55	2a-225	
	2a-226	

(continued)

No.	R ₁	X ₁ -X ₂ -X ₃
2a-227		
2a-228		
2a-229		
2a-230		
2a-231		
2a-232		
2a-233		
2a-234		
2a-235		
2a-236		
2a-237		

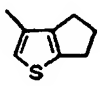
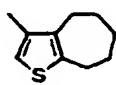
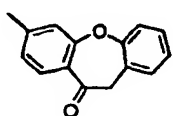
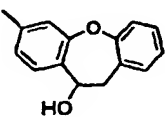
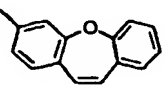
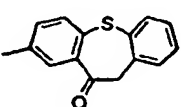
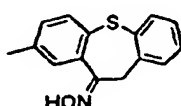
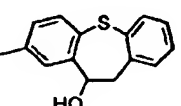
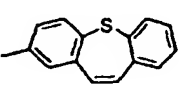
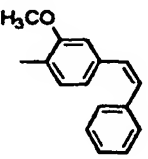
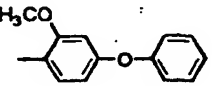
(continued)

No.	R ₁	X ₁ -X ₂ -X ₃
5 2a-238		
10 2a-239		
15 2a-240		
20 2a-241		
25 2a-242		
30 2a-243		
35 2a-244		
40 2a-245		
45 2a-246		
50 2a-247		
55 2a-248		

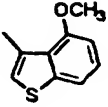
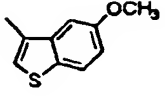
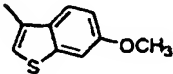
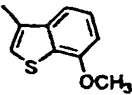
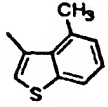
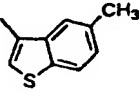
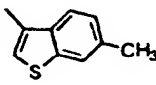
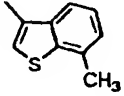
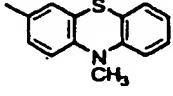
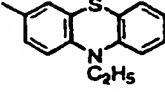
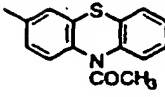
(continued)

No.	R ₁	X ₁ -X ₂ -X ₃
2a-249		
2a-250		
2a-251		
2a-252		
2a-253		
2a-254		
2a-255		
2a-256		
2a-257		
2a-268		

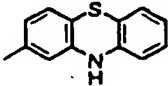
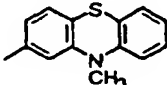
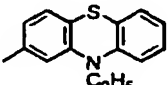
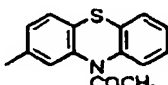
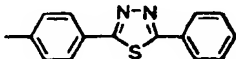
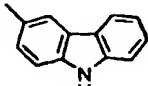
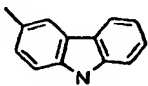
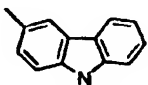
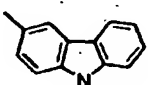
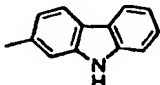
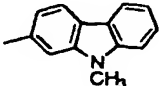
(continued)

No.	R ₁	X ₁ -X ₂ -X ₃
5	2a-269	
10	2a-270	
15	2a-271	
20	2a-272	
25	2a-273	
30	2a-274	
35	2a-275	
40	2a-276	
45	2a-277	
50	2a-258	
55	2a-259	

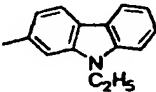
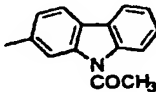
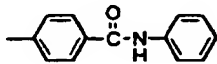
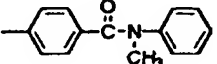
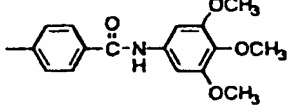
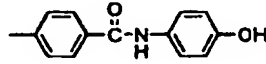
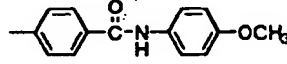
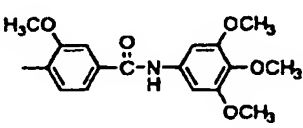
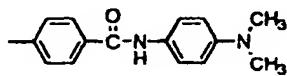
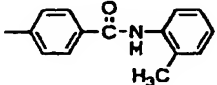
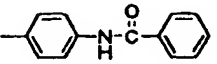
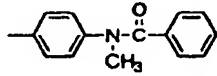
(continued)

No.	R ₁	X ₁ -X ₂ -X ₃
5	2a-260	
10	2a-261	
15	2a-262	
20	2a-263	
25	2a-264	
30	2a-265	
35	2a-266	
40	2a-267	
45	2a-278	
50	2a-279	
55	2a-280	

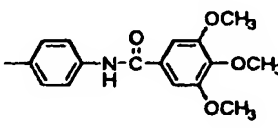
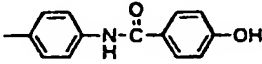
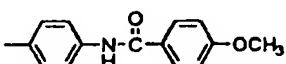
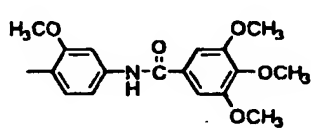
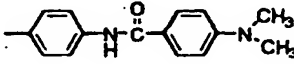
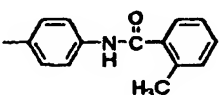
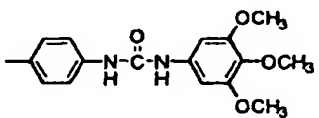
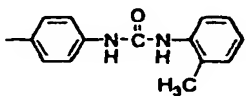
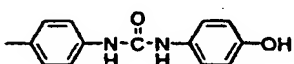
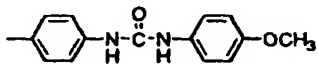
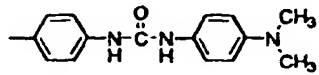
(continued)

No.	R ₁	X ₁ -X ₂ -X ₃
5 2a-281		
10 2a-282		
15 2a-283		
20 2a-284		
25 2a-285		
30 2a-286		
35 2a-287		
40 2a-288		
45 2a-289		
50 2a-290		
55 2a-291		

(continued)

No.	R ₁	X ₁ -X ₂ -X ₃
5	2a-292	
10	2a-293	
15	2a-294	
20	2a-295	
25	2a-296	
30	2a-197	
35	2a-298	
40	2a-299	
45	2a-300	
50	2a-301	
55	2a-302	
	2a-303	

(continued)

No.	R ₁	X ₁ -X ₂ -X ₃
2a-304		
2a-305		
2a-306		
2a-307		
2a-308		
2a-309		
2a-310		
2a-311		
2a-312		
2a-313		
2a-314		

(continued)

No.	R ₁	X ₁ -X ₂ -X ₃
-----	----------------	--

2a-315

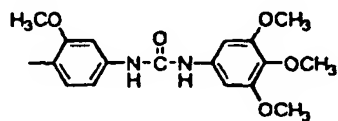
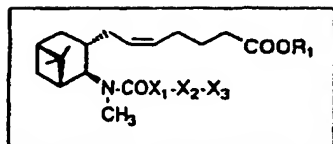
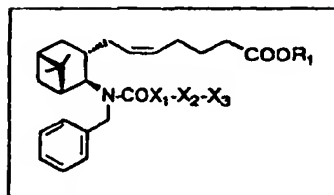


Table 2b



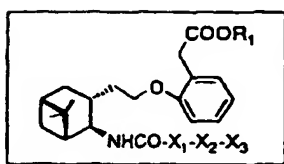
No.	R ₁	X ₁ -X ₂ -X ₃
2b-1	H	
2b-2	H	

Table 2c



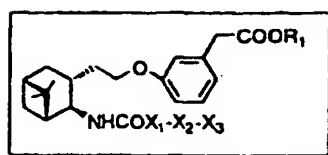
No.	R ₁	X ₁ -X ₂ -X ₃
2c-1	H	
2c-2	H	
2c-3	H	

Table 2d



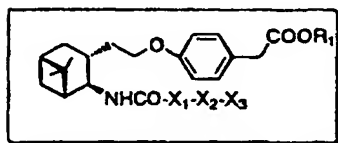
No.	R ₁	X ₁ -X ₂ -X ₃
2d-1	H	
2d-2	H	
2d-3	H	

Table 2e



No.	R ₁	X ₁ -X ₂ -X ₃
2e-1	H	
2e-2	H	
2e-3	H	

Table 2f



No.	R ₁	X ₁ -X ₂ -X ₃
2f-1	H	

(continued)



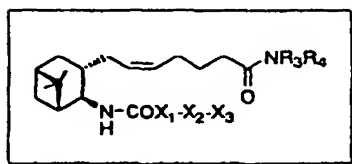
No.	R ₁	X ₁ -X ₂ -X ₃
2f-2	H	
2f-3	H	

Table 2g




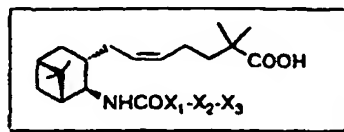

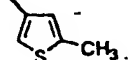

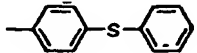
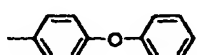
No.	R ₃	R ₄	X ₁ -X ₂ -X ₃
2g-1	H	SO ₂ CH ₃	

Table 2h



No.	X ₁ -X ₂ -X ₃
2h-1	
2h-2	
2h-3	
2h-4	
2h-5	

(continued)

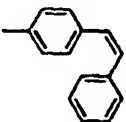
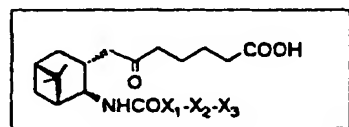
No.	$X_1-X_2-X_3$
2h-6	

Table 2i






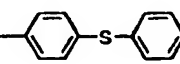
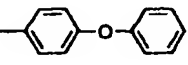
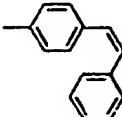
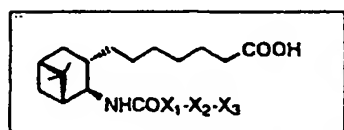
No.	$X_1-X_2-X_3$
2i-1	
2i-2	
2i-3	
2i-4	
2i-5	
2i-6	

Table 2j



(continued)


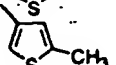
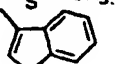
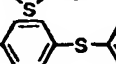

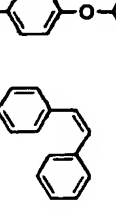
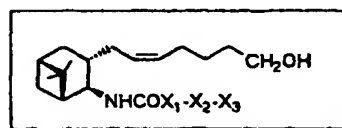

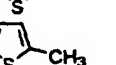
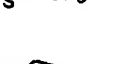


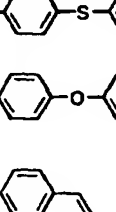
No.	$X_1-X_2-X_3$
2j-1	
2j-2	
2j-3	
2j-4	
2j-5	
2j-6	

Table 2k



No.	$X_1-X_2-X_3$
2k-1	
2k-2	
2k-3	
2k-4	
2k-5	
2k-6	

[0065] Physicochemical properties of compounds above are shown below. The compound number below corresponds

to that described in Tables above.

No.1k-1

5 [0066] $[\alpha]_D = -25.4^\circ$ (CHCl_3 , $c=1.08$, 23°C).

No.1k- 2

[0067] CDCl_3 200MHz

10 1.07-2.28(14H,m), 2.32(2H,t, $J=7.4\text{Hz}$), 2.63(1H,m), 3.63(3H,s), 3.93(1H,m), 5.30-5.52(2H,m), 6.35(1H,d, $J=7.0\text{Hz}$), 7.48-7.60(3H,m), 7.88-8.02(6H,m). IR(CHCl_3): 3438, 3002, 2946, 2868, 1727, 1652, 1514, 1485, 1363, 1310, 1245, 1154 /cm. $[\alpha]_D = -80.4^\circ$ (CHCl_3 , $c=1.01$, 24.0°C).

No.1k-3

15 [0068] CDCl_3 200MHz

1.10-2.26(14H,m), 2.37(2H,t, $J=7.2\text{Hz}$), 2.60(1H,m), 3.93(1H,m), 5.30-5.50(2H, m), 6.33 (1H,d, $J=7.5\text{Hz}$), 7.48-7.58(3H, m), 7.88-7.99 (6H,m). IR(CHCl_3): 3446, 3004, 2952, 2874, 1709, 1652, 1515, 1485, 1305, 1153 /cm. $[\alpha]_D = -96.4^\circ$ (CHCl_3 , $c=1.05$, 23.0°C).

20 No.1k- 4

[0069] CDCl_3 300MHz

25 1.05-2.17(14H,m), 2.38(2H,t, $J=7.2\text{Hz}$), 2.52(1H,m), 3.81(1H,m), 5.33-5.50(2H, m), 6.08(1H,d, $J=7.6\text{Hz}$), 7.39-7.53(3H,m), 7.57-7.62(6H,m). IR(CHCl_3): 3420, 3250, 3008, 2948, 2870, 2660, 2208, 1735(sh); 1705, 1640, 1500/c m. $[\alpha]_D = -21.9 \pm 0.6^\circ$ (CHCl_3 , $c=1.02$, 22°C).

No.1k-5

30 [0070] CDCl_3 300MHz

1.05-2.14(14H,m), 2.38(2H,t, $J=7.2\text{Hz}$), 2.51(1H,m), 3.81(1H,m), 5.34-5.46(2H, m), 6.07(1H,d, $J=7.6\text{Hz}$), 7.33-7.56(3H,m). IR(CHCl_3): 3422, 3250, 3010, 2950, 2876, 2664, 2558, 2210, 1735(sh), 1705, 1645, 1502, 1441, 1410, 1307, 1276/cm. $[\alpha]_D = -63.6 \pm 1.9^\circ$ (CHCl_3 , $c=0.56$, 22°C).

35 No.1k-6

[0071] CDCl_3 300MHz

40 1.04-2.24(14H,m), 2.36(2H,t, $J=7.5\text{Hz}$), 2.58(1H,m), 3.88(1H,m), 5.30-5.43(2H, m), 6.21(1H, d, $J=7.2\text{Hz}$), 7.41-7.49(3H, m), 7.73-7.77(2H,m). IR(CHCl_3): 3447, 3011, 2955, 1708, 1653, 1603, 1578, 1515, 1486, 1457, 1312, 1211, 1164/cm. $[\alpha]_D = -60.3^\circ$ (CHCl_3 , $c=1.00$, 23°C).

No.1k-7

45 [0072] CDCl_3 300MHz

1.04-2.22(14H,m), 2.36(2H, t, $J=7.2\text{Hz}$), 2.57 (1 H,m), 3.87 (1 H,m), 5.30-5.44(2H, m), 6.17(1H,d, $J=8.7\text{Hz}$), 6.99-7.40(7H, m), 7.73(2H,d, $J=7.5\text{Hz}$). IR(CHCl_3): 3449, 3013, 2955, 1739, 1708, 1651, 1609, 1588, 1522, 1487, 1243, 1227, 1169/cm. $[\alpha]_D = -60.2^\circ$ (CHCl_3 , $C=0.92$, 23°C).

50 No.1k-8

[0073] CDCl_3 300MHz

55 1.04-2.25(14H,m), 2.34(2H,t, $J=7.5\text{Hz}$), 2.56(1H,m), 3.87(1H,m), 5.30-5.44(2H, m), 6.19 (1 H, d, $J=7.5\text{Hz}$), 6.83-6.94 (6H, m), 7.69(2H, d, $J=8.7\text{Hz}$). IR(CHCl_3): 3599, 3455, 3012, 2955, 1711, 1644, 1604, 1577, 1524, 1507, 1492, 1290, 1236, 1197, 1170/cm. $[\alpha]_D = -47.7^\circ$ (CHCl_3 , $c=1.01$, 22°C).

No.1k-9

[0074] CDCl₃ 300MHz

1.04-2.20(14H,m), 2.31(3H,s), 2.36(2H,t,J=7.2Hz), 2.56(1H,m), 3.86(1H,m), 5.3 0-5.43(2H,m), 6.16(1H,d,J=7.2Hz),
 5 7.00-7.11(6H,m), 7.74(2H,d,J=8.7Hz).

IR(CHCl₃):3450,3010,2955,1750,1709,1651,1609,1596,1523,1489,1370,1247, 1227,1183/cm.[α]_D=-54.7° (CHCl₃,c=1.01,22°C).

No.1k-10

[0075] CDCl₃ 300MHz

1.04-2.22(14H,m), 2.35(2H,t,J=7.2Hz), 2.56(1H,m), 3.82(3H,s), 3.86(1H,m), 5.3 0-5.43(2H,m), 6.17(1H,d,J=6.9Hz),
 10 6.89-7.01(6H,m), 7.70(2H,d,J=8.7Hz).

IR(CHCl₃):3023,2955,1742,1708,1649,1613,1602,1577,1522,1507,1490,1227, 1210,1170/cm.[α]_D=-58.1° (CHCl₃,C=1.01,22°C).

No.1m-1

[0076] CDCl₃ 300MHz

1.06-2.25(14H,m), 2.32(2H,t,J=7.4Hz), 2.61(1H,m), 3.63(3H,s), 3.91(1H,m), 5.3 3-5.47(2H,m), 6.24(1H,d,J=6.9Hz),
 20 7.35-7.38(3H,m), 7.53-7.60(4H,m), 7.75-7.78(2H,m).

IR(CHCl₃):3438,3008,2946,2875,2212,1732,1650,1605,1519,1496/cm.[α]_D= +76° (CHCl₃,c=1.39,24°C)

No.1m- 2

[0077] CDCl₃ 300MHz

1.05-2.20(14H,m), 2.36(2H,t,J=6.2Hz), 2.59(1H,m), 3.89(1H,m), 5.29-5.48(2H, m), 6.26(1H,d,J=7.0Hz), 7.26-7.38(3H,m),
 30 7.52-7.60(4H,m), 7.73-7.77(2H,m).

IR(CHCl₃):3444,3012,2952,2874,2664,2214,1718(sh),1708,1649,1605,1520,1498/cm.[α]_D= +81.4° (CHCl₃,c=1.01,23°C)

No.1m-3

[0078] CDCl₃ 300MHz 1.06-2.23(14H,m), 2.32(2H,t,J=7.0Hz), 2.62(1H,m), 3.63(3H,s), 3.93(1H,m), 5.3 0-5.50(2H,m),
 35 6.28(1H,d,J=7.0Hz), 7.38-7.51(3H,m), 7.58-7.67(4H,m), 7.83-7.88(2H,m).

IR(CHCl₃):3438,3008,2948,2875,1783(w), 1727,1650,1608,1580(w), 1523,1501,1482/cm .[α]_D= +59° (CHCl₃,c=1.49,25°C)

No.1m-4

[0079] CDCl₃ 300MHz

1.08-2.25(14H,m), 2.36(2H,t,J=7.4Hz), 2.59(1H,m), 3.91(1H,m), 5.28-5.48(3H, m), 6.29(1H,d,J=7.4Hz), 7.38-7.50(3H,m),
 45 7.61-7.67(4H,m), 7.81-7.86(2H,m).

IR(CHCl₃):3436,3010,2948,2868,1727,1715(sh),1649,,16.15(w),1524,1502,1482,1372/cm.[α]_D= +72° (CHCl₃,c=0.98,25°C)

No.1m- 5

[0080] CDCl₃ 300MHz

1.09-2.20(14H,m), 2.32(2H,t,J=7.2Hz), 2.63(1H,m), 3.63(3H,s), 3.92(1H,m), 5.3 1-5.51(2H,m), 6.35(1H,d,J=7.0Hz),
 50 7.51-7.60(3H,m), 7.92-7.97(6H,m).

IR(CHCl₃):3436,3008,2946,2875,1727,1652,1608(w),1515,1484/cm.[α]_D= +82° (CHCl₃,c=0.99,25°C)

No.1m-6

[0081] CDCl₃ 300MHz

EP 0 837 052 B1

1.09-2.23(14H,m),2.37(2H,t,J=7.2Hz),2.60(1H,m),3.92(1H,m),5.30-5.49(2H, m),6.32(1H,d,J=7.4Hz),7.51-7.55(3H,m),
7.85-7.98(6H,m).

IR(CHCl₃):3436,3010,2950,2875,2670,1727.1715(sh),1650,1605(w),1515,148 4/cm.

[α]_D= +84° (CHCl₃,C=1.54,25°C)

5

No.1m-7

[0082] CDCl₃ 300MHz

1.03-2.18(14H,m),2.32(2H,t,J=7.4Hz),2.59(1H,m),3.64(3H,s),3.89(1H,m),5.2 9-5.49(2H,m),6.16(1H,d,J=7.8Hz),

10 6.98-7.06(4H,m),7.14-7.20(1H,m),7.34-7.4 1(2H,m),7.73-7.78(2H,m).

IR(CHCl₃):3438,3008,2946,2868,1727,1648,1610,1586,1519,1485/cm.

[α]_D= +54° (CHCl₃,c=1.29,25°C).

No.1m-8

15

[0083] CDCl₃ 300MHz

1.06-2.21(14H,m),2.36(2H,t,J=7.5Hz),2.58(1H,m),3.88(1H,m),5.31-5.46(2H, m),6.17(1H,d,J=6.9Hz),6.99-7.05(4H,m),

7.15-7.21(1H,m),7.36-7.41(2H,m),7. 72-7.75(2H,m).

IR(CHCl₃):3436,3010,2948.2868,2675,1730(sh),1709,1647,1608,1586,1520,1 485/cm.

20 [α]_D= +56° (CHCl₃,c=0.97,25°C)

No.1m-9

[0084] CDCl₃ 300MHz

25 1.05-2.18(14H,m),2.29-2.34(5H,m),2.59(1H,m),3.64(3H,s),3.89(1H,m),5.32-5. 46(2H,m),6.16(1H,d,J=7.5Hz),

7.00-7.11(6H,m),7.74-7.77(2H,m).

IR(CHCl₃):3440,3010,2946,2868,1729,1649,1595,1519,1488/cm.

[α]_D= +47° (CHCl₃,c=0.82,25°C).

30 No.1m-10

[0085] CDCl₃ 300MHz

1.04-2.20(14H,m),2.31-2.39(5H,m),2.57(1H,m),3.87(1H,m),5.28-5.47(2H,m), 6.17(1H, d,J=7.0Hz),6.99-7.12(6H,m),

7.72-7.76(2H,m).

35 IR(CHCl₃):3674,3572,3438,3010,2948,2868,2626,1748,1710,1648,1615,1595, 1520,1489/cm..

[α]_D= +51° (CHCl₃,c=0.91,25°C)

No.1m-11

40 [0086] CDCl₃ 300MHz

1.04-2.16(14H,m),2.31(2H,t,J=7.2Hz),2.59(1H,m),3.63(3H,s),3.89(1H,m),5.2 9-5.49(2H,m),6.24(1H,d,J=7.4Hz),6.54

(1H,s),6.83-6.93(6H,m),7.69-7.73(2H, m).

IR(CHCl₃):3674,3588,3438,3296,3010,2946,2868,1725,1646,1603,1520,1504, 1489/cm.

[α]_D= +51° (CHCl₃,c=0.91.25°C)

45

No.1m-12

[0087] CDCl₃ 300MHz

1.04-2.21(14H,m),2.33(2H,t,J=8.0Hz),2.56(1H,m),3.87(1H,m),5.28-5.48(2H, m),6.23(1H,d,J=8.0Hz),6.75(1H,m),

50 6.87-6.94(6H,m),7.66-7.71(2H,m),9.63(1 H,brs).

IR(CHCl₃):3674,3582,3436,3275,3010,2950,2868,2675,1727,1710(sh),1643,1 603,1522,1504,1490/cm.

[α]_D= +30° (CHCl₃,c=0.97,25°C)

No.1m- 13

55

[0088] CDCl₃ 300MHz

1.01-2.18(14H,m),2.31(2H,t,J=7.4Hz),2.58(1H,m),3.63(3H,s),3.82(3H,s),3.89 (1H,m),5.29-5.48(2H,m).6.14(1H,d,

J=7.0Hz),6.88-7.02(6H,m),7.70-7.74(2H, m).

EP 0 837 052 B1

IR(CHCl₃):3442,3402,3004,2946,2868,1727,1648,1600,1518,1499/cm.

[α]_D=+42° (CHCl₃,c=1.82,26°C)

No.1m-14

5

[0089] CDCl₃ 300MHz

1.05-2.21(14H,m),2.35(2H,t,J=7.2Hz),2.55(1H,m),3.82(3H,s),3.88(1H,m),5.2 7-5.46(2H,m),6.16(1H,d,J=7.2Hz),
6.88-7.02(6H,m),7.68-7.73(2H,m).

IR(CHCl₃):3438,3012,2948,2870,2650,1730(sh),1709,1647,1615(sh),1601,1519,1492/cm.

10

[α]_D=+64° (CHCl₃,c=0.70,25°C)

No.1m-15

[0090] CDCl₃ 300MHz

15

1.05-2.20(14H,m),2.29-2.36(5H,m),2.62(1H,m),3.63(3H,s),3.92(1H,m),5.30-5.50(2H,m),6.25(1H,d,J=7.2Hz),
7.16-7.21(2H,m),7.59-7.64(4H,m),7.83-7.87(2H,m).

IR(CHCl₃):3446,3010,2946,2868,1745(sh),1728,1650,1615,1525,1507,1486/cm.

[α]_D=+65.0° (CHCl₃,c=1.02,23°C)

20

No.1m-16

[0091] CDCl₃ 300MHz

1.08-2.21(14H,m),2.34-2.40(5H,m),2.59(1H,m),3.90(1H,m),5.29-5.48(2H,m),6.29(1H,d,J=7.0Hz),7.18(2H,d,
J=8.6Hz),7.58-7.64(4H,m),7.83(2H,d,J=8.2Hz).

25

IR(CHCl₃):3438,3012,2948,2870,2622,1749,1710,1649,1610,1526,1508,1487/cm.

[α]_D=+66° (CHCl₃,c=1.21,24°C)

No.1m-17

30

[0092] CDCl₃ 300MHz

1.06-2.19(14H,m),2.32(2H,t,J=7.2Hz),2.62(1H,m),3.63(3H,s),3.93(1H,m),5.30-5.50(2H,m),6.32(1H,d,J=7.6Hz),6.41
(1H,s),6.94(2H,d,J=9.0Hz),7.47(2H,d,J=9.0Hz),7.58(2H,d,J=8.6Hz),7.81(2H,d,J=8.6Hz).

IR(CHCl₃):3580,3434,3284,3010,2946,2868,1726,1646,1606,1528,1490/cm.

[α]_D=+62.4° (CHCl₃,c=1.01,23°C)

35

No.1m-18

[0093] CDCl₃+CD₃OD 300MHz

40

1.11-2.18(14H,m),2.32(2H,t,J=7.4Hz),2.59(1H,m),3.88(1H,m),5.30-5.49(2H,m),6.55(1H,d,J=7.0Hz),6.92(2H,d,
J=8.6Hz),7.47(2H,d,J=8.6Hz),7.59(2H,d,J=8.6Hz),7.79(2H,d,J=8.2Hz).

IR(Nujol):3398,3175,2725,1696,1635,1601,1531,1510/cm.

[α]_D=+99.5° (CH₃OH,c=1.011,25°C)

No.1m-19

45

[0094] CDCl₃ 300MHz

1.05-2.20(14H,m),2.32(2H,t,J=7.4Hz),2.61(1H,m),3.63(3H,s),3.86(3H,s),3.94 (1H,m),5.30-5.50(2H,m),6.24(1H,d,
J=7.0Hz),6.99(2H,d,J=8.6Hz),7.53-7.63(4H,m),7.82(2H,d,J=8.6Hz).

IR(CHCl₃):3440,3006,2946,2875,1726,1649,1606,1527,1510,1489/cm.

50

[α]_D=+68° (CHCl₃,c=0.88,26°C)

No.1m-20

[0095] CDCl₃ 300MHz

55

1.09-2.20(14H,m),2.35(2H,t,J=7.3Hz),2.58(1H,m),3.85(3H,s),3.89(1H,m),5.2 8-5.48(2H,m),6.35(1H,d,J=7.2Hz),6.98
(2H,d,J=8.8Hz),7.51-7.61(4H,m),7.81(2H,d,J=8.4Hz),8.34(1H,brs).

IR(CHCl₃):3446,3012,2952,2881,2640,1730(sh),1707,1647,1606,1527,1510,1489/cm.

[α]_D=+83° (CHCl₃,c=1.00,25°C).

No.1m- 21

[0096] CDCl₃ 300MHz

1.05-2.14(14H,m), 2.37(2H,t,J=7.2Hz), 2.51(1H,m), 3.81(1H,m), 5.34-5.46(2H, m), 6.11(1H,d,J=7.5Hz), 7.33-7.48(3H,m), 7.53-7.55(2H,m).

IR(CHCl₃):3420,3250,3008,2948,2870,2660,2210,1735(sh),1705,1645,1503,1 441,1409/cm.[α]_D=+59.2±1.0° (CHCl₃,c=1.023, 22°C).

No.1m - 22

[0097] CDCl₃ 300MHz

1.05-2.17(14H, m), 2.37(2H, t,J=7.2Hz), 2.52(1H,m), 3.82(1H,m), 5.32-5.47(2H, m), 6.20(1H,d,J=7.6Hz), 7.38-7.53(3H, m), 7.58-7.61(6H,m), 9.11(1H,brs).

IR(CHCl₃):3420,3250,3010,2984,2870,2675,2208,1730(sh),1705,1640,1500,1 406/cm.[α]_D=+57.4° (CHCl₃,c=1.83,23°C).

No.1m- 23

[0098] CDCl₃ 300MHz

1.05-2.18(14H,m), 2.31(2H,t,J=7.5Hz), 2.60(1H,m), 3.63(3H,s), 3.90(1H,m), 5.3 2-5.47(2H,m), 6.22(1H,d,J=6.9Hz), 7.40-7.49(3H,m), 7.76-7.79(2H,m).

IR(CHCl₃):3438,3008,2946,2868,1727,1651,1603,1585,1512,1484/cm.[α]_D=+52° (CHCl₃,c=1.49,25°C).

No.1m- 24

[0099] CDCl₃ 300MHz

1.05-2.21(14H,m), 2.36(2H,t,J=7.2Hz), 2.57(1H,m), 3.89(1H,m), 5.28-5.47(2H, m), 6.22(1H,d,J=7.0Hz), 7.39-7.55(3H,m), 7.73-7.79(2H,m).

IR(CHCl₃):3676,3572,3436,3010,2948,2875,1730(sh),1709,1650,1600,1580,1 514,1484/cm.[α]_D=+57° (CHCl₃,c=0.97,26°C).

No.1m- 25

[0100] CDCl₃ 300MHz

1.04-2.18(14H,m), 2.28-2.35(5H,m), 2.59(1H,m), 3.62(3H,s), 3.88(1H,m), 5.29-5. 49(2H,m), 6.20(1H,d,J=7.2Hz), 7.15(2H, d,J=9.0Hz), 7.80(2H,d,J=8.8Hz).

IR(CHCl₃):3436,3010,2946,2868,1752,1727,1653,1602,1519,1491/cm.[α]_D=+53° (CHCl₃,c=1.63,25°C).

No.1m- 26

[0101] CDCl₃ 300MHz

1.05-2.19(14H,m), 2.32-2.38(5H,m), 2.56(1H,m), 3.88(1H,m), 5.29-5.47(2H,m), 6.25(1H,d,J=7.4Hz), 7.15(2H,d, J=9.0Hz), 7.78(2H,d,J=8.6Hz).

IR(CHCl₃):3434,3016,3006,2948,2880,2622,1752,1730(sh),1710,1651,1605,1 520,1492/cm.[α]_D=+58° (CHCl₃,c=3.68,24°C)

No.1m - 27

[0102] CDCl₃ 300MHz

1.05-2.16(14H,m), 2.30(2H,t,J=7.5Hz), 2.57(1H,m), 3.62(3H,s), 3.87(1H,m), 5.2 7-5.47(2H,m), 6.32(1H,d,J=7.4Hz), 6.85 (2H,d,J=8.6Hz), 7.62(2H,d,J=8.6Hz), 8. 35(1H,s

IR(CHCl₃):3580,3450,3216,3010,2946,2868,1726,1640,1608,1584,1528,14961 cm.[α]_D=+56.2° (CHCl₃,c=0.713,23°C)

No.1m-28

[0103] CDCl₃ 200MHz

1.10-2.25(14H,m), 2.32(2H,t,J=7.2Hz), 2.55(1H,brs), 3.82-3.93(1H,m), 5.27-5.47(2H,m), 6.25(1H,d,J=7.4Hz), 6.86(2H,d,
J=8.6Hz), 7.62(2H,d,J=8.6Hz).

IR(CHCl₃):3438,3242,2675,1730(sh),1708,1639,1607,1585/cm.

No.1m-29

[0104] CDCl₃ 300MHz

1.05-2.18(14H,m), 2.31(2H,t,J=7.4Hz), 2.58(1H,m), 3.64(3H,s), 3.85(3H,s), 3.89(1H,m), 5.29-5.48(2H,m), 6.14(1H,d,
J=6.6Hz), 6.92(2H,d,J=9.0Hz), 7.74(2H,d,J=9.0Hz).

IR(CHCl₃):3445,3008,2946,2868,1727,1646,1606,1578,1623,1493/cm.[α]_D=+53° (CHCl₃, c=2.03, 24°C)

No.1m-30

[0105] CDCl₃ 300MHz

1.04-2.21(14H,m), 2.36(2H,t,J=7.3Hz), 2.56(1H,m), 3.85(3H,s), 3.88(1H,m), 5.27-5.46(2H,m), 6.15(1H,d,J=7.2Hz), 6.92
(2H,d,J=8.6Hz), 7.73(2H,d,J=8.6Hz)

IR(CHCl₃):3440,3010,2950,2870,2645,1727,1710(sh),1646,1606,1575,1524,1494/cm.[α]_D=+62° (CHCl₃, c=1.10, 24°C)

No.1m-31

[0106] CDCl₃+CD₃OD 300MHz

1.16-2.20(14H,m), 2.31(2H,t,J=7.2Hz), 2.59(1H,m), 3.85(1H,m), 5.31-5.51(2H,m), 7.13-7.21(1H,m), 7.31-7.42(2H,m),
7.68-7.93(6H,m).

IR(Nujol):3344,3175,2715,2675,1699,1631,1566/cm.

[α]_D=+67° (CH₃OH, c=1.01, 24°C)

No.1m-32

[0107] CDCl₃ 200MHz

1.09-2.23(14H,m), 2.33(2H,t,J=7.1Hz), 2.57(1H,brs), 3.40-3.93(9H,m), 4.41(1H,brs), 5.29-5.48(2H,m), 6.44(1H,d,
J=7.4Hz), 7.43(2H,d,J=8.2Hz), 7.80(2H,d,J=7.8Hz).

IR(CHCl₃):3434,3354,1726,1720(sh),1660(sh),1626/cm.

No.1m-33

[0108] CDCl₃ 200MHz

1.14-2.25(14H,m), 2.37(2H,t,J=7.3Hz), 2.64(1H,brs), 3.93-4.01(1H,m), 5.30-5.51(2H,m), 6.47(1H,d,J=7.4Hz), 7.63-7.74
(2H,m), 7.79(2H,s), 7.89-7.93(1H,m), 8.00(1H,dd,J=2.3,1.0Hz), 8.30(1H,d,J=1.0Hz), 8.65-8.73(2H,m).

IR(CHCl₃):3450,2675,1728,1707,1649,1528,1509/cm.[α]_D=+82.8±1.2° (CHCl₃, c=1.01, 23°C)

No.2a-1

[0109] [α]_D=+69.0° (MeOH, c=1.01, 25°C)

No.2a-2

[0110] CDCl₃ 300MHz

0.99(1H,d,J=10.2Hz), 1.15 and 1.24(each 3H,each s), 1.50-2.50(14H,m), 4.30(1H,m), 5.35-5.52(2H,m), 6.32(1H,d,
J=8.7Hz), 7.36-7.49(3H,m), 7.58-7.62(2H,m), 7.66 and 7.80(each 2H,each d,J=8.7Hz).

IR(CHCl₃):3116,3014,2925,2870,2663,1708,1651,1610,1524,1504,1484,1472 /cm.[α]_D= +64.1° (MeOH, c=1.02, 25°C)

No.2a-3

[0111] $[\alpha]_D = +76.6^\circ$ (MeOH, c=1.18, 26°C).

5 No.2a-4

[0112] CDCl₃ 300MHz

0.99(1H,d,J=10.2Hz), 1.15 and 1.25(each 3H,each s), 1.64-2.51(14H,m), 4.3 1(1H,m), 5.36-5.53(2H,m), 6.33(1H,d, J=8.4z), 7.50-7.56(3H,m), 1.85-7.98(6H, m).

10 IR(CHCl₃):3515,3452,3014,2925,2870,1740,1708,1654,1517,1486,1470 /cm. $[\alpha]_D = +79.5^\circ$ (MeOH, c=1.18, 22°C).

No.2a-5

15 [0113] CD₃OD 300MHz

0.98(1H,d,J=9.9Hz), 1.18 and 1.25(each 3H,each s), 1.56-1.71(3H,m), 1.98-2.40(11H,m), 4.17(1H,m), 5.41-5.52(2H,m), 7.52-7.61(3H,m), 7.91-8.01(6H,m).

IR(KBr):3416,3063,2983,2921,2869,1704,1643,1566,1518,1488,1408 /cm.

 $[\alpha]_D = +62.0^\circ$ (MeOH, c=1.00, 25°C).

20

No.2a-6

[0114] $[\alpha]_D = +64.1^\circ$ (MeOH, c=1.01, 25°C).

25 No.2a-7

[0115] $[\alpha]_D = +65.3^\circ$ (MeOH, c=0.99, 25°C).

No.2a-8

30

[0116] $[\alpha]_D = +74.0^\circ$ (MeOH, c= 1.01, 25°C).

No.2a-9

35 [0117] $[\alpha]_D = +71.0^\circ$ (MeOH, c=1.10, 25°C).

No.2a-10

[0118] $[\alpha]_D = +74.7^\circ$ (MeOH, c=1.00, 25°C).

40

No.2a-11

[0119] $[\alpha]_D = +72.1^\circ$ (MeOH, c=1.00, 25°C).

45 No.2a-12

[0120] $[\alpha]_D = +53.1^\circ$ (CHCl₃, c=1.01, 26°C):

m.p.155.0-156.0°C

50 No.2a-13

[0121] CDCl₃ 300MHz

0.98(1H,d,J=10.2Hz), 1.18 and 1.25(each 3H,each s), 1.63-2.40(14H,m), 4.3 0(1H,m), 5.46-5.58(2H,m), 6.44(1H,d, J=8.4Hz), 7.49 and 7.77(each 2H,each d,J=8.7Hz), 7.54(1H,s).

55 IR(CHCl₃):3689,3378,3028,3014,2924,1713,1652,1602,1522,1496 /cm. $[\alpha]_D = +78.3^\circ$ (MeOH, c=0.84, 25°C).

m.p.205.0-206.0°C

No.2a-14

[0122] $[\alpha]_D^{+72.5}$ (MeOH, c=1.07, 25°C).

5 No.2a-15

[0123] CDCl₃ 300MHz

0.99(1H, d, J=9.9Hz), 1.14 and 1.24(each 3H, each s), 1.55-2.44(14H, m), 4.27(1H, m), 5.30-5.50(2H, m), 6.29(1H, d, J=9.0Hz), 7.11 and 7.20(each 1H, each d, J=16.2Hz), 7.29-7.55(5H, m), 7.57 and 7.72(each 2H, each d, J=8.7Hz).

10 IR(CHCl₃): 3453, 3083, 3022, 3013, 2925, 2870, 1708, 1650, 1607, 1560, 1522, 1496 /cm. $[\alpha]_D^{+72.3}$ (MeOH, c=1.00, 27°C).

m.p. 115.0-117.0°C

No.2a-16

15

[0124] CDCl₃ 300MHz

0.92(1H, d, J=10.2Hz), 1.11 and 1.23(each 3H, each s), 1.50-2.48(14H, m), 3.62(3H, s), 4.29(1H, m), 5.30-5.50(2H, m), 6.20(1H, d, J=8.7Hz), 6.59 and 6.68(each 1H, each d, J=12.3Hz), 7.23(5H, s), 7.29 and 7.59(each 2H, each d, J=8.1Hz).

IR(CHCl₃): 3453, 3024, 3016, 2924, 2870, 1730, 1651, 1607, 1520, 1495 /cm.20 $[\alpha]_D^{+56.8}$ (MeOH, c=1.04, 24°C).

No.2a-17

[0125] CDCl₃ 300MHz

25 0.97(1H, d, J=10.2Hz), 1.11 and 1.23(each 3H, each s), 1.50-2.38(14H, m), 4.26(1H, m), 5.30-5.50(2H, m), 6.23(1H, d, J=8.4Hz), 6.59 and 6.70(each 1H, each d, J=12.3Hz), 7.23(5H, s), 7.30 and 7.57(each 2H, each d, J=8.7Hz).

IR(CHCl₃): 3452, 3081, 3019, 3014, 2925, 2870, 2665, 1708, 1650, 1607, 1521, 1495 /cm. $[\alpha]_D^{+61.6}$ (MeOH, c=1.00, 27°C).

30 No.2a-18

[0126] CDCl₃ 300MHz

0.97(1H, d, J=10.2Hz), 1.11 and 1.23(each 3H, each s), 1.50-2.50(14H, m), 3.61(3H, s), 4.31(1H, m), 5.35-5.51(2H, m), 6.33(1H, d, J=8.4Hz), 7.48-7.64(4H, m), 7.79-7.83(2H, m), 7.91(1H, dt, J=1.5 and 7.8Hz), 8.01(1H, dt, J=1.5 and 7.8Hz),

35 8.13(1H, t, J=1.5Hz).

IR(CHCl₃): 3450, 3026, 3013, 2925, 2870, 1730, 1659, 1600, 1510 /cm. $[\alpha]_D^{+56.0}$ (MeOH, c=1.01, 25°C).

No.2a-19

40

[0127] CDCl₃ 300MHz

0.95(1H, d, J=9.9Hz), 1.14 and 1.21(each 3H, each s), 1.53-2.60(14H, m), 4.25(1H, m), 5.35-5.64(2H, m), 7.21(1H, d, J=7.8Hz), 7.49-7.68(4H, m), 7.76-7.84(3H, m), 8.25(1H, m), 8.43(1H, m).

IR(CHCl₃): 3382, 3196, 3025, 3015, 2925, 2870, 1725, 1652, 1599, 1577, 1521 /cm.45 $[\alpha]_D^{+55.9}$ (MeOH, c=1.00, 25°C).

No.2a-20

[0128] CDCl₃ 300MHz

50 0.98(1H, d, J=10.2Hz), 1.13 and 1.24(each 3H, each s), 1.50-2.50(14H, m), 3.62(3H, s), 4.31(1H, m), 5.35-5.51(2H, m), 6.24(1H, d, J=8.4Hz), 7.40-7.52(3H, m), 7.71-7.76(2H, m).

IR(CHCl₃): 3453, 3025, 3013, 2925, 2870, 1730, 1753, 1579, 1514, 1486 /cm. $[\alpha]_D^{+61.2}$ (MeOH, c=1.04, 25°C).

55 No.2a-21

[0129] CDCl₃ 300MHz

0.98(1H, d, J=10.2Hz), 1.13 and 1.23(each 3H, each s), 1.52-2.50(14H, m), 4.28(1H, m), 5.34-5.51(2H, m), 6.27(1H, d,

EP 0 837 052 B1

J=8.7Hz), 7.41-7.53(3H,m), 7.71-7.74(2H, m).
 IR(CHCl₃): 3452, 3063, 3027, 3014, 2925, 2871, 1708, 1652, 1578, 1515, 1486 /cm.
 [α]_D= +62.0° (MeOH, c=1.01, 27°C).

5 No.2a-22

[0130] d₆-DMSO 300MHz
 0.86(1H,d,J=9.9Hz), 1.10 and 1.16(each 3H,each s), 1.42-1.52(3H,m), 1.85-2.46(11H,m), 3.98(1H,m), 5.32-5.43(2H,m),
 7.41(3H,m), 7.88(2H,d,J=6.6Hz), 8.19 (1H,d,J=6.6Hz).
 10 IR(KBr): 3367, 3060, 2984, 2922, 2868, 1634, 1563, 1529, 1487/cm.
 [α]_D=+47.7° (MeOH, c=1.00, 25°C).

No.2a-23

15 [0131] [α]_D=+62.7° (MeOH, c=1.01, 27°C).

No.2a-24

[0132] CDCl₃ 300MHz
 20 0.99(1H,d,J=10.2Hz), 1.14 and 1.25(each 3H,each s), 1.52-2.50(14H,m), 4.3 1(1H,m), 5.36-5.52(2H,m), 6.34(1H,d,
 J=8.4Hz), 7.47-7.52(2H,m), 7.59-7.64(1H, m), 7.78-7.83(6H,m).
 IR(CHCl₃): 3449, 3027, 3013, 2925, 2869, 1708, 1656, 1599, 1518, 1493 /cm.
 [α]_D= +63.1° (MeOH, c=1.00, 25°C).

25 No.2a.25

[0133] [α]_D=+35.1° (MeOH, c=1.00, 25°C).

No.2a-26

30

[0134] [α]_D=+35.5° (MeOH, c=1.02, 25°C).

No.2a-27

35 [0135] CDCl₃ 300MHz
 0.97(1H,d,J=10.2Hz), 1.12 and 1.23(each 3H,each s), 1.52-2.50(14H, m), 3.6 3(3H,s), 4.29(1H,m), 5.36-5.51(2H,m), 6.18
 (1H,d,J=8.4Hz), 7.01 and 7.71 (each 2H,each d,J=8.7Hz.), 6.98-7.05(2H,m), 7.16(1H,t,J=7.5Hz), 7.34-7.41(2 H,m).
 IR(CHCl₃): 3455, 3024, 3016, 2924, 2870, 1730, 1651, 1588, 1520, 1487 /cm. [α]_D=+56.4° (MeOH, c=1.01, 25°C).

40 No.2a.28

[0136] CDCl₃ 300MHz
 0.98(1H,d,J=10.2Hz), 1.12 and 1.23(each 3H,each s), 1.52-2.50(14H,m), 4.2 6(1H,m), 5.34-5.51(2H,m), 6.20(1H,d,
 J=9.0Hz), 7.01 and 7.70(each 2H, each d,J=9.0Hz.), 6.98-7.15(2H,m), 7.17(1H,t,J=7.5Hz), 7.34-7.40(2H,m).
 45 IR(CHCl₃): 3454, 3031, 3018, 2925, 2870, 1708, 1650, 1588, 1523, 1487/cm.
 [α]_D= +56.2° (MeOH, c=1.00, 25°C).

No.2a-29

50 [0137] [α]_D=+53.0° (MeOH, c=1.03, 25°C).

No.2a-30

[0138] CDCl₃ 300MHz
 55 0.97(1H,d,J=10.2Hz), 1.10 and 1.23(each 3H,each s), 1.52-2.50(14H,m), 4.2 5(1H,m), 5.30-5.50(2H,m), 6.23(1H,d,
 J=8.7Hz), 6.36(1H,s), 7.26-7.39(10H,m), 7. 60 and 7.68(each 2H,each d,J=8.4Hz.).
 IR(CHCl₃): 3451, 3088, 3064, 3029, 3014, 2925, 2869, 1707, 1652, 1522, 1495 /cm.
 [α]_D=+54.2° (MeOH, c=1.00, 25°C).

No.2a-31

[0139] CDCl₃ 300MHz

0.98(1H,d,J=10.2Hz),1.14 and 1.24(each 3H,each s),1.50-2.50(14H,m),3.6 3(3H,s),4.31(1H,m),5.30-5.50(2H,m),6.26
 5 (1H,d,J=8.4Hz),6.90(1H,t,J=7.4Hz), 7.13(1H,d,J=8.7Hz),7.29(2H,t,J=8.0Hz),7.67-7.75(5H,m),7.82(1H,s).

IR(Nujol):3380,3244,1723,1638,1601,1578,1535,1495 /cm.

[α]_D=+73.6° (MeOH,c=0.50,26°C).

m.p.133.0-134.0°C

10 No.2a.32

[0140] [α]_D=+56.1° (MeOH,c=1.02,26°C).

No.2a-33

15

[0141] CDCl₃ 300MHz

0.95(1H,d,J=10.2Hz),1.10 and 1.21(each 3H,each s),1.50-2.50(14H,m),4.25 (1H,m),5.13(2H,s),5.30-5.70(3H,m),6.41
 (1H, d,J=8.2Hz),6.89 (1H, s); 7.09(1H, s),7.17 and 7.72(each 2H,each d,J=8.2Hz),7.62(1H,s).

IR(CHCl₃):3450,3125,3031,3013,2925,2870,2467,1917,1708,1654,1615,1575, 1523,1497 /cm.

20 [α]_D=+55.2° (MeOH,c=1.01,26°C).

No.2a-34

[0142] [α]_D=+72.9° (MeOH,c=1.03,25°C).

25

No.2a-35

[0143] CDCl₃ 300MHz

0.98(1H,d,J=10.2Hz),1.13 and 1.24(each 3H,each s),1.52-2.48(14H,m),4.2 8(1H,m),5.35-5.51(2H,m).6.28
 30 (1H,d,J=8.7Hz),7.34-7.37(3H,m),7.52-7.55(2H, m),7.58 and 7.71(each 2H,each d,J=8.7Hz).

IR(CHCl₃):3515,3452,3030,3012,2925,2870,1739,1708,1652,1607,1555,1521, 1497 /cm.[α]_D=+74.3° (MeOH,c=1.01,25°C).

No.2a-36

35

[0144] [α]_D=+23.4° (MeOH,c=1.07,25°C).

No.2a-37

40

[0145] CDCl₃ 300MHz

0.83(1H,d,J=10.5Hz),0.95 and 1.18(each 3H,each s),1.44-2.46(14H,m),3.9 2(1H,m),5.34-5.52(3H,m),7.26-7.54(9H,m),
 7.62(1H,s).

IR(CHCl₃):3432,3310,3189,3023,3014,2924,2870,1704,1610,1594,1523,1487 /cm.[α]_D=+25.3° (MeOH,c=1.00,26°C).

45

No.2a-38

[0146] [α]_D=+70.9° (MeOH,c=1.02,25°C).

50 No.2a.39

[0147] [α]_D=+70.6° (MeOH,c=1.01,25°C).

No.2a-40

55

[0148] [α]_D=+74.7° (MeOH,c=1.00,25°C).

No.2a-41

[0149] $[\alpha]_D^{25} = +72.1^\circ$ (MeOH, c=1.01, 24°C).

5 No.2a-42

[0150] $[\alpha]_D^{25} = +69.2^\circ$ (MeOH, c=1.00, 25°C).

No.2a-43

10

[0151] $[\alpha]_D^{25} = +70.8^\circ$ (MeOH, c=1.00, 25°C).

No.2a-44

15

[0152] $[\alpha]_D^{26} = +60.4^\circ$ (MeOH, c=1.00, 26°C).

No.2a-45

[0153] CDCl₃ 300MHz

20

0.97(1H,d,J=9.9Hz), 1.13 and 1.23(each 3H, each s), 1.55-2.52(14H,m), 4.29(1H,m), 5.34-5.54(2H,m), 6.33(1H,d, J=9.0Hz), 7.10(1H,t, J=7.4Hz), 7.34(2H,t, J=7.4Hz), 7.52(2H,m), 7.68 and 7.75(each 2H, each d, J=8.4Hz), 7.80(1H,s), 8.10(1H,s), 10.09(1H,s).

IR(CHCl₃): 3393, 3195, 3093, 3033, 3013, 2925, 2870, 1698, 1656, 1598, 1537, 1498 /cm.[0153] $[\alpha]_D^{25} = +59.4^\circ$ (MeOH, c=1.01, 24°C).

25

No.2a-46

[0154] $[\alpha]_D^{25} = +63.5^\circ$ (MeOH, c=1.00, 25°C).

30 No.2a-47

[0155] CDCl₃ 300MHz

0.97(1H,d,J=9.9Hz), 1.12 and 1.23(each 3H, each s), 1.54-2.48(14H,m), 4.29(1H,m), 5.35-5.52(2H,m), 6.32(1H,d, J=8.7Hz), 7.26(1H,m), 7.41(2H,t, J=7.8Hz), 7.64(2H,d, J=7.5Hz), 7.73 and 7.77(each 2H, each d, J=8.4Hz), 7.95(1H,s), 9.20(1H,s), 10.38(1H,s).

35

IR(CHCl₃): 3450, 3339, 3003, 2992, 2925, 2870, 1706, 1653, 1596, 1523, 1495 /cm.[0155] $[\alpha]_D^{25} = +63.3^\circ$ (MeOH, c=1.00, 25°C).

No.2a-48

40

[0156] $[\alpha]_D^{25} = +63.8^\circ$ (MeOH, c=1.00, 24°C).

No.2a-49

45

[0157] CDCl₃ 300MHz

1.00(1H,d,J=10.5Hz), 1.17 and 1.26(each 3H, each s), 1.55-2.52(14H,m), 4.34(1H,m), 5.36-5.54(2H,m), 6.35(1H,d, J=9.0Hz), 7.50-7.62(3H,m), 7.90 and 8.33(each 2H, each d, J=8.4Hz), 8.21(2H,m)

IR(CHCl₃): 3451, 3029, 3022, 3016, 2925, 2870, 1708, 1655, 1542, 1508, 1498, 1471, 1459 /cm.[0157] $[\alpha]_D^{25} = +63.5^\circ$ (MeOH, c=1.02, 25°C):

50

m.p. 135.0-137.0 °C

No.2a-50

[0158] $[\alpha]_D^{25} = +68.9^\circ$ (MeOH, c=1.01, 24°C).

55

No.2a-51

[0159] d₆-DMSO 300MHz

EP 0 837 052 B1

0.87(1H,d,J=9.9Hz), 1.10 and 1.17(each 3H,each s), 1.40-1.60(3H,m), 1.90-2.40(11H,m), 3.98(1H,m), 5.35-5.46(2H,m), 7.64(1H,s), 7.65 and 7.91(each 2H, each d,J=8.7Hz), 8.06(1H,d,J=6.0Hz), 9.32(1H, brs).
IR(KBr):3385, 2962, 1734, 1707, 1632, 1529, 1498 /cm.
[α]_D=+68.4° (MeOH,c=1.01,24°C).

5

No.2a-52

[0160] [α]_D=+76.2° (MeOH,c=1.01,24°C).

10

No.2a-53

[0161] [α]_D=+73.9° (MeOH,c=1.02,24°C).

No.2a-54

15

[0162] [α]_D=+68.1° (MeOH,c=1.00,24°C).

No.2a-55

20

[0163] [α]_D=+67.8° (MeOH,c=1.00,24°C).

No.2a-56

[0164] [α]_D=+65.4° (MeOH,c=1.03,25°C).

25

No.2a-57

[0165] [α]_D=+63.4° (MeOH,c=1.01,24°C).

30

No.2a-58

[0166] [α]_D=+66.6° (MeOH,c=1.01,24°C).

No.2a-59

35

[0167] [α]_D=+65.5° (MeOH,c=1.00,24°C).

No.2a-60

40

[0168] [α]_D=+60.9° (MeOH,c=1.02,25°C).

No.2a-61

[0169] CDCl₃ 300MHz

45

0.97(1H,d,J=10.0Hz), 1.10 and 1.22(each 3H,each s), 1.50-2.50(14H,m), 4.26(1H,m), 5.30-5.54(2H,m), 6.28(1H,d, J=8.6Hz), 6.60 and 6.82(each 1H,each d,J=12.4Hz), 7.12(2H,d,J=6.0Hz), 7.25 and 7.62(each 2H,each d,J=8.6Hz), 8.47 (2H,d,J=6.0Hz).

IR(CHCl₃):3452,3027,3019,3013,2925,2870,2980,1708,1651,1606,1520,1494 /cm.

[α]_D=+61.6° (MeOH,c=1.01,25°C).

50

No.2a-62

[0170] [α]_D=+72.0° (MeOH,c=0.93,25°C).

55

No.2a-63

[0171] CDCl₃ 300MHz

0.99(1H,d,J=10.2Hz), 1.14 and 1.24(each 3H,each s), 1.50-2.50(14H,m), 4.29(1H,m), 5.36-5.55(2H,m), 6.35(1H,d,

EP 0 837 052 B1

J=9.1Hz), 7.04 and 7.27(each 1H, each d, J=16.5Hz), 7.37(2H, d, J=6.6Hz), 7.56 and 7.76(each 2H, each d, J=8.4Hz), 8.57 (2H, d, J=6.6Hz).

IR(CHCl₃): 3452, 3024, 3018, 3014, 2925, 2870, 2470, 1933, 1708, 1652, 1605, 1521, 1496 /cm.

[α]_D=+69.2° (MeOH, c=1.01, 25°C).

5

No.2a-64

[0172] [α]_D=+56.9° (MeOH, c=1.24, 25°C).

10

No.2a-65

[0173] CDCl₃ 300MHz

0.98(1H, d, J=10.5Hz), 1.12 and 1.23(each 3H, each s), 1.54-2.46(14H, m), 4.2 7(1H, m), 5.23(2H, s), 5.34-5.52(2H, m), 6-.26 (1H, d, J=8.4Hz), 7.32-7.45(5H, m), 7.64 and 7.71(each 2H, each d, J=8.4Hz), 8.15(1H, s).

15

IR(CHCl₃): 3452, 3088, 3065, 3032, 3013, 2925, 2870, 1708, 1653, 1611, 1559, 1522, 1496 /cm.

[α]_D=+61.0° (MeOH, c=0.91, 25°C).

No.2a-66

20

[0174] [α]_D=+76.0° (MeOH, c=1.01, 25°C).

No.2a-67

[0175] CDCl₃ 300MHz

25

0.98(1H, d, J=10.4Hz), 1.14 and 1.24(each 3H, each s), 1.54-2.46(14H, m), 4.2 8(1H, m), 5.32-5.53(2H, m), 6.27(1H, d, J=8.6Hz), 6.92-7.31(each 1H, each d, J= 16.4Hz), 7.02(1H, dd, J=5.8 and 3.6Hz), 7.12(1H, d, J=3.6Hz), 7.24(1H, d, J=5.8 Hz), 7.51 and 7.70(each 2H, each d, J=8.4Hz).

IR(CHCl₃): 3453, 3029, 3013, 2925, 2870, 1739, 1650, 1604, 1524, 1515, 1494 /cm.

[α]_D=+76.2° (MeOH, c=1.00, 24°C).

30

m.p. 104.0-106.0°C

No.2a-68

[0176] [α]_D=+57.7° (MeOH, c=1.01, 25°C).

35

No.2a-69

[0177] CDCl₃ 300MHz

40

0.99(1H, d, J=10.2Hz), 1.14 and 1.24(each 3H, each s), 1.54-2.48(14H, m), 4.2 8(1H, m), 5.34-5.53(2H, m), 6.29(1H, d, J=9.0Hz), 6.54-6.74(each 1H, each d, J= 12.0Hz), 7.02(1H, dd, J=4.8 and 3.3Hz), 6.97(1H, dd, J=3.3 and 1.2Hz), 7.13(1H, dd, J=4.8 and 1.2Hz), 7.44 and 7.70(each 2H, each d, J=8.7Hz).

IR(CHCl₃): 3453, 3025, 3010, 2925, 2870, 1708, 1650, 1607, 1559, 1523, 1493 /cm.

[α]_D=+58.4° (MeOH, c=1.00, 25°C).

45

No.2a-70

[0178] [α]_D=+48.6° (MeOH, c=1.00, 25°C).

No.2a-71

50

[0179] CDCl₃ 300MHz

0.98(1H, d, J=10.2Hz), 1.12 and 1.23(each 3H, each s), 1.52-2.46(14H, m), 2.3 1(3H, s), 4.26(1H, m), 5.33-5.52(2H, m), 6.20 (1H, d, J=9.3Hz), 7.02-7.11(6H, m), 7.70(2H, d, J=9.0Hz).

IR(CHCl₃): 3460, 3031, 3022, 3011, 2925, 2870, 1750, 1708, 1650, 1608, 1597, 1523, 1490 /cm.

55

[α]_D=+48.9° (MeOH, c=1.01, 25°C).

No.2a-72

[0180] $[\alpha]_D^{25} = +51.2^\circ$ (MeOH, c=1.02, 25°C).

5 No.2a-73

[0181] CDCl₃ 300MHz

0.97(1H,d,J=9.9Hz), 1.11 and 1.23(each 3H, each s), 1.54-2.48(14H,m), 4.27(1H,m), 5.32-5.52(2H,m), 6.24(1H,d, J=9.0Hz), 6.83-6.94(6H,m), 7.65(2H,d,J=9.0Hz).

10 IR(CHCl₃): 3598, 3451, 3199, 3033, 3012, 2925, 2870, 1708, 1642, 1604, 1524, 1507, 1491 /cm.[α]_D²⁵ = +52.2° (MeOH, c=1.01, 25°C).

No.2a-74

15 [0182] $[\alpha]_D^{25} = +51.5^\circ$ (MeOH, c=0.92, 25°C).

No.2a-75

[0183] CDCl₃ 300MHz

20 0.97(1H,d,J=10.2Hz), 1.11 and 1.23(each 3H, each s), 1.55-2.46(14H,m), 3.8 2(3H,s), 4.25(1H,m), 5.32-5.52(2H,m), 6.19 (1H,d,J=8.7Hz), 6.89-7.01(6H,m), 7.65-7.68(2H,m).

IR(CHCl₃): 3450, 3025, 3008, 2925, 2870, 2837, 1741, 1649, 1612, 1521, 1505, 1490 /cm.[α]_D²⁵ = +51.1° (MeOH, c=1.00, 25°C).

25 No.2a-76

[0184] $[\alpha]_D^{25} = +60.4^\circ$ (MeOH, c=0.98, 25°C).

No.2a-77

30

[0185] CDCl₃ 300MHz

0.99(1H,d,J=10.5Hz), 1.15 and 1.24(each 3H, each s), 1.54-2.48(14H,m), 2.3 4(3H,s), 4.29(1H,m), 5.32-5.54(2H,m), 6.32 (1H,d,J=8.4Hz), 7.19 and 7.60 (each 2H, each d, J=8.4Hz), 7.63 and 7.79(each 2H, each d, J=8.4Hz).

IR(CHCl₃): 3452, 3027, 3012, 2925, 2870, 1751, 1709, 1651, 1611, 1560, 1527, 1509, 1489 /cm.35 [α]_D²⁵ = +61.2° (MeOH, c=1.00, 25°C).

No.2a-78

[0186] $[\alpha]_D^{25} = +67.4^\circ$ (MeOH, c=1.01, 25°C).

40

No.2a-79

[0187] CDCl₃ 300MHz

45 0.99(1H,d,J=10.2Hz), 1.15 and 1.24(each 3H, each s), 1.54-2.54(14H,m), 4.3 1(1H,m), 5.32-5.54(2H,m), 6.36(1H,d, J=8.2Hz), 6.93 and 7.48(each 2H, each d, J=8.6Hz), 7.59 and 7.75(each 2H, each d, J=8.4Hz).

IR(CHCl₃): 3593, 3448, 3192, 3030, 3010, 2925, 2870, 1708, 1644, 1608, 1591, 1559, 1530, 1516, 1491 /cm.[α]_D²⁵ = +65.8° (MeOH, c=1.01, 25°C).

No.2a-80

50

[0188] $[\alpha]_D^{25} = +66.9^\circ$ (MeOH, c=1.01, 25°C).

No.2a-81

55

[0189] CDCl₃ 300MHz

0.99(1H,d,J=10.5Hz), 1.15 and 1.24(each 3H, each s), 1.54-2.48(14H,m), 3.8 6(3H,s), 4.29(1H,m), 5.34-5.52(2H,m), 6.20 (1H,d,J=8.7Hz), 6.99 and 7.55 (each 2H, each d, J=9.0Hz), 7.61 and 7.77(each 2H, each d, J=8.7Hz).

IR(CHCl₃): 3450, 3009, 2925, 2870, 2838, 1740, 1708, 1650, 1608, 1557, 1528, 1512, 1491 /cm.

$[\alpha]_D = +66.2^\circ$ (MeOH, c=1.01, 25°C).

No.2a-82

5 **[0190]** $[\alpha]_D = +57.7^\circ$ (MeOH, c=1.02, 24°C).

No.2a-83

[0191] CDCl₃ 300MHz

10 0.97(1H, d, J=10.2Hz), 1.12 and 1.23(each 3H, each s), 1.54-2.48(14H, m), 2.3 3(3H, s), 4.26(1H, m), 5.32-5.52(2H, m), 6.25 (1H, d, J=8.7Hz), 7.16 and 7.75 (each 2H, each d, J=8.7Hz).

IR(CHCl₃):3452, 3030, 3022, 3012, 2925, 2870, 1754, 1709, 1654, 1604, 1585, 1522, 1493 /cm.

$[\alpha]_D = +57.4^\circ$ (MeOH, c=1.01, 24°C).

15 No.2a-84

[0192] $[\alpha]_D = +57.8^\circ$ (MeOH, c=1.01, 24°C).

No.2a-85

20

[0193] CDCl₃ 300MHz

0.95(1H, d, J=10.2Hz), 1.12 and 1.22(each 3H, each s), 1.54-2.48(1.4H, m), 4.2 5(1H, m), 5.32-5.52(2H, m), 6.280H, d, J=8.7Hz), 6.87 and 7.57(each 2H, each d, J=9.0Hz).

IR(CHCl₃):3590, 3450, 3166.3019, 3012, 2925, 2871.1708, 1637, 1608, 1583, 1531, 1498 /cm.

25 $[\alpha]_D = +56.0^\circ$ (MeOH, c=1.01, 24°C).

No.2a.86

[0194] $[\alpha]_D = +59.3^\circ$ (MeOH, c=1.01, 22°C).

30

No.2a-87

[0195] CDCl₃ 300MHz

0.98(1H, d, J=10.0Hz), 1.13 and 1.23(each 3H, each s), 1.54-2.48(14H, m), 3.8 5(3H, s), 4.25(1H, m), 5.32-5.53(2H, m), 6.19(1H, d, J=8.8Hz), 6.93 and 7.69 (each 2H, each d, J=9.0Hz).

35

IR(CHCl₃):3450, 3030, 3017, 3012, 2925, 2870, 2840, 1740, 1708, 1647, 1606, 1575, 1525, 1496 /cm.

$[\alpha]_D = +58.2^\circ$ (MeOH, c=0.99, 22°C).

No.2a-88

40

[0196] $[\alpha]_D = +50.9^\circ$ (MeOH, c=1.02, 25°C).

No.2a-89

[0197] CDCl₃ 300MHz

0.99(1H, d, J=10.2Hz), 1.18 and 1.26(each 3H, each s), 1.56-2.48(14H, m), 4.2 9(1H, m), 5.36-5.54(2H, m), 7.03(1H, d, J=8.7Hz), 7.21(1H, s), 7.43(2H, m), 7.74(1 H, ddd, J=1.8, 6.9 and 8.7Hz), 8.22(1H, dd, J=1.8 and 8.1Hz).

45

IR(CHCl₃):3443, 3087, 3023, 3014, 2925, 2870, 1708, 1685, 1658, 1630, 1517, 1466 /cm .

$[\alpha]_D = +57.1^\circ$ (MeOH, c=1.01, 22°C).

50

m.p.117.0-118.0°C

No.2a.90

[0198] $[\alpha]_D = +54.1^\circ$ (MeOH, c=1.01, 22°C).

55

No.2a.91

[0199] CDCl₃ 300MHz

EP 0 837 052 B1

0.97(1H,d,J=10.2Hz), 1.13 and 1.23(each 3H,each s), 1.52-2.46(14H,m), 4.2 4(1H,m), 5.34-5.52(2H,m), 6.49-6.53(12H, m), 7.11(1H,dd,J=0.9 and 3.6Hz), 7.4 4(1H,dd,J=0.9 and 1.8Hz).

IR(CHCl₃):3437,3033,3022,3014,2925,2870,1739,1708,1655,1595,1520,1472 /cm.

[α]_D=+55.0° (MeOH,c=1.00,22°C).

5

No.2a-92

[0200] [α]_D=+50.3° (MeOH,c=1.00,22°C).

10

No.2a-93

[0201] CDCl₃ 300MHz

0.95(1H,d,J=10.5Hz), 1.12 and 1.23(each 3H,each s), 1.52-2.46(14H,m), 4.2 5(1H,m), 5.34-5.52(2H,m), 6.12(1H,d, J=8.7Hz), 7.07(1H,dd,J=3.9 and 5.1Hz), 7.45-7.48(2H,m).

15

IR(CHCl₃):3450,3023,3011,2925,2870,1739,1708,1645,1531,1501,1471 /cm.

[α]_D=+49.1° (MeOH,c=1.02,24°C).

No.2a-94

20

[0202] [α]_D=+51.5° (MeOH,c=1.00,24°C).

No.2a.95

[0203] CDCl₃ 300MHz

25

0.96(1H,d,J=10.5Hz), 1.11 and 1.23(each 3H,each s), 1.52-2.46(14H,m), 4.2 5(1H,m), 5.34-5.56(2H,m), 6.14(1H,d, J=8.7Hz), 7.34(2H,d,J=2.0Hz), 7.85(1H,t, J=2.0Hz).

IR(CHCl₃):3452,3114,3030,3013 2925,2870,1708,1649,1535,1498,1471/cm.

[α]_D=+55.5° (MeOH,c=1.00,25°C).

m.p.87.0-88.0°C

30

No.2a-96

[0204] CD₃OD 300MHz

35

0.94(1H,d,J=10.2Hz), 1.13 and 1.22(each 3H,each s), 1.50-1.76(3H,m), 1.94-2.39(11H,m), 4.11(1H,m), 5.39-5.49(2H, m), 7.43-7.51(2H,m), 8.05(1H,m).

IR(KBr):3369,3084,2985,2921,2868,1630,1566,1538,1503 /cm.

[α]_D=+38.8° (MeOH,c=1.01,22°C).

No.2a.97

40

[0205] CD₃OD 300MHz

0.93(1H,d,J=9.9Hz), 1.13 and 1.22(each 3H,each s), 1.48-1.58(3H,m), 1.96-2. 36(11H,m), 4.10(1H,m), 5.35-5.50(2H,m), 7.42-7.51(2H,m), 8.06(1H,m).

IR(KBr):3447,3087,2987,2922,2868,1629,1545,1501 /cm.

45

[α]_D=+52.9° (MeOH,c=1.01,24°C).

No.2a.98

[0206] [α]_D=+53.2° (MeOH,c=1.02,23°C).

50

No.2a-99

[0207] CDCl₃ 300MHz

55

0.97(1H,d,J=10.2Hz), 1.12 and 1.22(each 3H,each s), 1.26-2.45(24H,m), 4.2 5(2H,m), 5.34-5.52(2H,m), 6.18(1H,d, J=8.7Hz), 6.91 and 7.66(each 2H,each d,J=9.0Hz).

IR(CHCl₃):3455,3029,3019,2939,2862,1738,1709,1645,1605,1523,1494 /cm.

[α]_D=+51.4° (MeOH,c=1.00,23°C).

EP 0 837 052 B1

No.2a-100

[0208] $[\alpha]_D^{25} = +49.3^\circ$ (MeOH, c=1.00, 24°C).

5 No.2a-101

[0209] $[\alpha]_D^{25} = +51.3^\circ$ (MeOH, c=1.00, 24°C).

No.2a-102

10

[0210] $[\alpha]_D^{25} = +48.8^\circ$ (MeOH, c=1.01, 23°C).

No.2a-103

15

[0211] CDCl₃ 300MHz

0.94(1H, d, J=10.2Hz), 1.12 and 1.22(each 3H, each s), 1.52-2.46(14H, m), 2.48(3H, d, J=0.3Hz), 4.20(1H, m), 5.32-5.54(2H, m), 6.46(1H, brs), 7.12(1H, d, J=9.0 Hz).

IR(CHCl₃): 3415, 3144, 3029, 3011, 2926, 2871, 1708, 1671, 1598, 1538, 14564 /cm

$[\alpha]_D^{25} = +49.6^\circ$ (MeOH, c=1.01, 23°C).

20

No.2a-104

[0212] $[\alpha]_D^{25} = +77.0^\circ$ (MeOH, c=1.02, 23°C).

25

No.2a-105

[0213] CDCl₃ 300MHz

93(1H, d, J=9.9Hz), 1.09 and 1.21(each 3H, each s), 1.51-2.44(14H, m), 3.90(6 H, s), 4.20(1H, m), 5.38-5.50(2H, m), 5.87(1H, d, J=9.0Hz), 6.25 and 7.54 (each 1H, each d, J=15.6Hz), 6.84(1H, d, J=8.1Hz), 7.03(1H, d, J=1.8Hz), 7.09(1 H, dd, J=1.8 and 8.1Hz).

30

IR(CHCl₃): 3439, 3028, 3012, 2937, 2871, 2841, 1739, 1708, 1661, 1620, 1600, 1513 /cm.

$[\alpha]_D^{25} = +77.3^\circ$ (MeOH, c=1.01, 23°C).

No.2a-106

35

[0214] $[\alpha]_D^{25} = +67.0^\circ$ (MeOH, c=1.00, 25°C)

No.2a.107

40

[0215] $[\alpha]_D^{25} = +66.6^\circ$ (MeOH, c=1.01, 24°C).

m.p. 168.0-170.0°C

No.2a-108

45

[0216] $[\alpha]_D^{25} = +61.8^\circ$ (MeOH, c=1.00, 22°C).

No.2a-109

[0217] CDCl₃ 300MHz

50

0.96(1H, d, J=10.2Hz), 1.10 and 1.22(each 3H, each s), 1.51-2.45(14H, m), 4.25(1H, m), 5.33-5.49(2H, m), 6.21(1H, d, J=8.7Hz), 7.25 and 7.60(each 2H, each d, J=8.7Hz), 7.33-7.41(5H, s).

IR(CHCl₃): 3453, 3062, 3028, 3014, 2925, 2870, 1739, 1708, 1651, 1594, 1557, 1515, 1481 /cm.

$[\alpha]_D^{25} = +61.0^\circ$ (MeOH, c=1.01, 22°C).

55

No.2a-110

[0218] CD₃OD 300MHz

0.94(1H, d, J=9.9Hz), 1.13 and 1.22(each 3H, each s), 1.54-2.37(14H, m), 4.12(1H, m), 5.38-5.49(2H, m), 7.25 and 7.68

EP 0 837 052 B1

(each 2H, each d, J=8.7Hz), 7.41(5H, s)
 IR(KBr): 3435, 3058, 2986, 2920, 2866, 1635, 1595, 1562, 1521, 1482, 1439, 1411 /cm.
 $[\alpha]_D^{25} = +47.3^\circ$ (MeOH, c=1.01, 23°C).

5 No.2a-111

[0219] $[\alpha]_D^{25} = +65.6^\circ$ (MeOH, c=1.01, 24°C).

No.2a-112

10

[0220] CDCl₃ 300MHz

0.97(1H, d, J=10.2Hz), 1.12 and 1.23(each 3H, each s), 1.51-2.46(14H, m), 4.2 7(1H, m), 5.35-5.50(2H, m), 6.22(1H, d, J=8.4Hz), 7.40 and 7.66(each 2H, each d, J=9.0 Hz).

IR(CHCl₃): 3439, 3028, 3012, 2937, 2871, 2841, 1739, 1708, 1661, 1620, 1600, 1513 /cm.

15

$[\alpha]_D^{25} = +65.6^\circ$ (MeOH, c=1.01, 22°C)

No.2a-113

[0221] $[\alpha]_D^{25} = 59.6^\circ$ (MeOH, c=1.00, 24°C).

20

No.2a-114

[0222] CDCl₃ 300MHz

0.98(1H, d, J=10.2Hz), 1.12 and 1.24(each 3H, each s), 1.52-2.46(14H, m), 4.2 9(1H, m), 5.35-5.51(2H, m), 6.28(1H, d, J=8.4Hz), 7.70 and 7.83(each 2H, each d, J=8.4Hz).

25

IR(CHCl₃): 3439, 3028, 3012, 2937, 2871, 2841, 1739, 1708, 1661, 1620, 1600, 1513 /cm.

$[\alpha]_D^{25} = +60.6^\circ$ (MeOH, c=1.01, 22°C).

No.2a-115

30

[0223] $[\alpha]_D^{25} = +59.7^\circ$ (MeOH, c=0.99, 24°C).

No.2a-116

35

[0224] CDCl₃ 300MHz

0.97(1H, d, J=10.2Hz), 1.12 and 1.23(each 3H, each s), 1.52-2.46(14H, m), 2.3 9(3H, s), 4.27(1H, m), 5.33-5.51(2H, m), 6.24(1H, d, J=9.0Hz), 7.23 and 7.62 (each 2H, each d, J=8.4Hz).

IR(CHCl₃): 3439, 3028, 3012, 2937, 2871, 2841, 1739, 1708, 1661, 1620, 1600, 1513 /cm.

40

$[\alpha]_D^{25} = +59.7^\circ$ (MeOH, c=0.99, 24°C).

No.2a-117

[0225] $[\alpha]_D^{25} = +56.7^\circ$ (MeOH, c= 1.00, 23°C).

45

No.2a-118

[0226] CDCl₃ 300MHz

0.96(1H, d, J=10.2Hz), 1.11 and 1.23(each 3H, each s), 1.53-2.44(14H, m), 4.2 3(1H, m), 5.34-5.51(2H, m), 6.02(2H, s), 6.13(1H, d, J=8.7Hz), 6.83(1H, dd, J=1.2 and 7.8Hz), 7.22.7.25(2H, m).

50

IR(CHCl₃): 3453, 3031, 3020, 3012, 2924, 2870, 1740, 1708, 1650, 1619, 1605, 1519, 1504, 1480 /cm.

$[\alpha]_D^{25} = +57.2^\circ$ (MeOH, c=1.02, 23°C).

No.2a-119

55

[0227] CDCl₃ 300MHz

0.96(1H, d, J=10.5Hz), 1.07 and 1.23(each 3H, each s), 1.51-2.44(14H, m), 2.3 2(3H, s), 4.26(1H, m), 5.37-5.52(2H, m), 6.40(1H, d, J=9.0Hz), 7.09(1H, m), 7.30(1H, m), 7.46(1H, m), 7.66(1H, m).

IR(CHCl₃): 3443, 3028, 3012, 2925, 2870, 1766, 1747, 1709, 1657, 1607, 1516, 1479 /cm.

$[\alpha]_D = +53.2^\circ$ (MeOH, c=0.99, 21°C).

No.2a-120

5 [0228] CDCl_3 300MHz
0.98(1H, d, J=10.2Hz), 1.14 and 1.24(each 3H, each s), 1.53-2.44(14H, m), 4.3 0(1H, m), 5.35-5.52(2H, m), 6.42(1H, d, J=8.7Hz), 6.85(1H, m), 6.99(1H, dd, J=1.2 and 8.4Hz), 7.27(1H, m), 7.39(1H, m).
IR(CHCl₃): 3463, 3033, 3021, 3014, 2992, 2924, 2870, 1708, 1643, 1597, 1523, 1488 /cm.
10 $[\alpha]_D = +46.3^\circ$ (MeOH, c=1.01, 21°C).

No.2a-121

[0229] CDCl_3 300MHz
0.98(1H, d, J=10.2Hz), 1.14 and 1.23(each 3H, each s), 1.47-2.47(14H, m), 3.9 5(3H, s), 4.31(1H, m), 5.32-5.50(2H, m), 6.98
15 (1H, dd, J=0.9 and 8.4Hz), 7.09(1H, ddd, J=0.9, 7.7 and 8.4Hz), 7.45(1H, m), 8.19(1H, dd, J=2.1 and 8.1Hz), 8.32(1 H, d, J=9.0Hz).
IR(CHCl₃): 3400, 3078, 3028, 3020, 3007, 2924, 2870, 2842, 1736, 1708, 1640, 1600, 1536, 1483, 1470 /cm.
 $[\alpha]_D = +38.1^\circ$ (MeOH, c=1.02, 23°C).

20 No.2a-122

[0230] $[\alpha]_D = +42.3^\circ$ (MeOH, c=0.99, 23°C).

No.2a-123

25 [0231] $[\alpha]_D = +38.7^\circ$ (MeOH, c=1.00, 21°C).

No.2a-124

30 [0232] $[\alpha]_D = +45.0^\circ$ (MeOH, c=1.01, 21°C).
m.p. 119.0-120.0°C

No.2a-125

35 [0233] $[\alpha]_D = +49.8^\circ$ (MeOH, c=1.01, 22°C).

No.2a-126

[0234] CDCl_3 300MHz
40 0.97(1H, d, J=10.2Hz), 1.11 and 1.23(cach 3H, each s), 1.52-2.47(14H, m), 4.2 6(1H, m), 5.34-5.50(2H, m), 6.22(1H, d, J=8.7Hz), 7.55-7.61(4H, m).
IR(CHCl₃): 3400, 3078, 3028, 3020, 3007, 2924, 2870, 2842, 1736, 1708, 1640, 1600, 1536, 1483, 1470 /cm.
 $[\alpha]_D = +63.0^\circ$ (MeOH, c=1.01, 23°C).

45 No.2a-127

[0235] CDCl_3 300MHz
0.91(1H, d, J=10.2Hz), 1.10 and 1.20(each 3H, each s), 1.50-2.42(14H, m), 4.2 3(1H, m), 5.31-5.51(2H, m), 6.45(1H, d, J=8.4Hz), 7.01(1H, t, J=7.4Hz), 7.22-7.27(2H, m), 7.33-7.40(4H, m), 7.53(2H, d, J=9.0.Hz), 8.30 and 8.48(each 1H, each s)
50 IR(CHCl₃): 3452, 3028, 3022, 3015, 2925, 2870, 1708, 1654, 1590, 1514, 1478 /cm.
 $[\alpha]_D = +59.5^\circ$ (MeOH, c=1.01, 23°C).

No.2a-128

55 [0236] d_6 -DMSO 300MHz
0.84(1H, d, J=9.9Hz), 1.06 and 1.19(each 3H, each s), 1.37-2.37(14H, m), 3.79(1H, m), 5.35-5.51 (2H, m), 6.08(1 H, d, J=8.7Hz), 6.85-6.90(1H, m), 7.18-7.23(2H, m), 7.35-7.38(2H, m), 8.42(1H, s), 12.00(1H, s).
IR(Nujol): 3395, 3345, 2925, 2866, 2623, 2506, 1697, 1658, 1638, 1597, 1557 /cm.

$[\alpha]_D^{25} = +26.0^\circ$ (MeOH, c=1.01, 23°C).
m.p. 164.0-166.0°C

No.2a-129

[0237] CDCl_3 300MHz

1.01(1H,d,J=10.0Hz), 1.17 and 1.25(each 3H,each s), 1.54-2.52(14H,m), 4.3 4(1H,m), 5.36-5.57(2H,m), 6.42(1H,d, J=8.6Hz), 7.51-7.60(2H,m), 7.77(1H,dd, J =1.8 and 8.6Hz), 7.85-7.96(3H,m), 8.24(1H,brs).

IR(CHCl_3): 3451, 3060, 3028, 3010, 2925, 2870, 1708, 1652, 1629, 1600, 1517, 1502 /cm.

$[\alpha]_D^{25} = +68.6^\circ$ (MeOH, c=1.00, 22°C).

No.2a-130

[0238] CDCl_3 300MHz

1.02(1H,d,J=10.2Hz), 1.04 and 1.26(each 3H,each s), 1.54-2.52(14H,m), 4.4 1(1H,m), 5.41-5.58(2H,m), 6.14(1H,d, J=9.0Hz), 7.43-7.59(4H,m), 7.85-7.92(2H, m), 8.27(1H,dd, J=1.8 and 7.2Hz).

IR(CHCl_3): 3436, 3032, 3010, 2924, 2870, 2664, 1708, 1652, 1512, 1498 /cm.

$[\alpha]_D^{25} = +93.9^\circ$ (MeOH, c=1.00, 22°C)

m.p. 94.0-96.0°C

No.2a-131

[0239] $[\alpha]_D^{25} = +50.2^\circ$ (MeOH, c=0.95, 21°C).

No.2a-132

[0240] $[\alpha]_D^{25} = +10.9^\circ$ (MeOH, c=0.92, 21°C).

No.2a-133

[0241] $[\alpha]_D^{25} = +60.4^\circ$ (MeOH, c=1.00, 21°C).

No.2a-134

[0242] $[\alpha]_D^{25} = +38.5^\circ$ (MeOH, c=1.01, 23°C).

No.2a-135

[0243] $[\alpha]_D^{25} = +52.5^\circ$ (MeOH, c=1.01, 23°C).

m.p. 180.0-182.0°C

No.2a-136

[0244] $[\alpha]_D^{25} = +35.3^\circ$ (MeOH, c=1.02, 23°C).

m.p. 79.0-80.0°C

No.2a-137

[0245] CDCl_3 300MHz

0.97(1H,d,J=10.2Hz), 1.11 and 1.22(each 3H,each s), 1.43(3H,t; J=6.9Hz), 1.52-2.44(14H,m), 4.03(2H,q, J=6.9Hz), 4.26(1H,m), 5.33-5.50(2H,m), 6.19(1H,d, J=8.7Hz), 6.88-7.00(6H,m), 7.65-7.68(2H,m).

IR(CHCl_3): 3455, 3031, 3024, 3014, 2988, 2925, 2870, 1741, 1708, 1649, 1602, 1521, 1504, 1490 /cm.

$[\alpha]_D^{25} = +52.0^\circ$ (MeOH, c=1.01, 23°C).

No.2a-138

[0246] CDCl_3 300MHz

0.97(1H,d,J=10.2Hz), 1.11 and 1.22(each 3H,each s), 1.35(6H,d, J=6.0Hz), 1.53-2.46(14H,m), 4.25(1H,m), 4.51(1H,m),

EP 0 837 052 B1

5.33-5.50(2H,m),6.12(1H,d,J=9.0Hz),6.87-6.99(6H,m),7.65-7.68(2H,m).
IR(CHCl₃):3454,3031,3014,2980,2925,2870,1741,1708,1649,1602,1522,1490 /cm.
[α]_D=+500° (MeOH,c=1.05,22°C).

5 No.2a-139

[0247] CDCl₃ 300MHz
1.00(1H,d,J=10.2Hz),1.16 and 1.24(each 3H,each s),1.59-2.52(14H,m),4.3 1(1H,m),5.40-5.53(2H,m),6.36(1H,d,
J=8.7Hz),6.70(1H,d,J=1.5Hz),7.12(1H, m),7.30(1H,m),7.47(1H,dd,J=0.6 and 8.1Hz),7.61(1H,d,J=8.4Hz).
10 IR(CHCl₃):3449,3243,3029,3022,3013,2925,2871,1707,1631,1542,1505 /cm. [α]_D=+63.4° (MeOH,c=1.00,23°C).
m.p.178.0-179.0°C

No.2a-140

15 [0248] CDCl₃ 300MHz
0.97(1H,d,J=10.2Hz),1.18 and 1.23(each 3H,each s),1.57-2.50(14H,m),4.3 5(1H,m),5.32-5.55(2H,m),6.42(1H,d,
J=8.7Hz),6.70(1H,d,J=1.5Hz),7.21-7.24(2H m),7.46(1H,m),7.76(1H,m),7.86(1H,d,J=3.0Hz),10.20(1H,s)
IR(CHCl₃):3465,3010,2924,1739,1604,1546,1504 /cm.
[α]_D=+39.4° (MeOH,c=1.01,22°C).
20 m.p.167.0-168.0°C

No.2a-141

[0249] CDCl₃ 300MHz
25 0.99(1H,d,J=10.2Hz),1.14 and 1.24(each 3H,each s),1.55-2.44(14H,m),3.8 4(3H,s),4.27(1H,m),5.34-5.52(2H,m),6.28
(1H,d,J=9.0Hz),6.91 and 7.47 (each 2H,each d,J=9.0Hz),6.98 and 7.14(each 1H, each d,J=16.5Hz),7.54 and 7.70(each
2H,eachd,J=8.7Hz).
IR(CHCl₃):3453,3025,3015,2925,2870,2839,1740,1708,1649,1602,1510,1493, 1470 /cm.
[α]_D=+73.4° (MeOH,c=1.02,22°C).
30 m.p.155.0-157.0°C

No.2a-142

[0250] CDCl₃ 300MHz
35 0.97(1H,d,J=10.2Hz),1.11 and 1.23(each 3H,each s),1.52-2.45(14H,m),3.7 9(3H,s),4.27(1H,m),5.34-5.50(2H,m),6.24
(1H,d,J=9.0Hz),6.49 and 6.62 (each 1H each d,J=12.3Hz),6.77 and 7.16(each 2H, each d,J=8.7Hz),7.32 and 7.59(each
2H, each d,J=8.1Hz).
IR(CHCl₃):3453,3025,3014,2925,2870,2839,1739,1708,1649,1606,1510, 1494 /cm.
[α]_D=+60.7° (MeOH,c=0.99,22°C).
40 m.p.155.0-157.0°C

No.2a-143

[0251] [α]_D=+57.3° (MeOH,c=1.01,23°C).

45 No.2a-144

[0252] [α]_D=+12.2° (MeOH,c=1.00,23°C).
m.p.114.0-116.0°C

50 No.2a-145

[0253] CDCl₃ 300MHz
0.95(1H,d,J=10.2Hz),1.10 and 1.21(each 3H,each s),1.52-2.44(14H,m),4.2 5(1H,m),5.33-5.49(2H,m),6.37(1H,d,
J=8.7Hz),7.45-7.47(3H,m),7.62-7.66(2H, m),7.69 and 7.80(each 2H,each d, J=7.5Hz,).
55 IR(CHCl₃):3449,3058,3027,3012,2925,2870,1708,1655,1513,1481,1043 /cm.
[α]_D=+61.0° (MeOH,c=1.01,23°C).

No.2a-146

[0254] CDCl₃ 300MHz

0.95(1H,d,J=10.5Hz),1.09 and 1.21(each 3H,each s),1.50-2.41(14H,m),4.2 5(1H,m),5.33-5.49(2H,m),6.33(1H,d,
J=8.4Hz),7.49-7.61(3H,m),7.91-7.92(2H, m),7.82 and 7.97(each 2H,each d,J=8.7Hz,).

IR(CHCl₃):3447,3029,3023,3015,2925,2870,1708,1660,1514,1484,1321,1161 /cm.[α]_D=+62.0° (MeOH,c=1.00,22°C).

No.2a-147

[0255] CDCl₃ 300MHz

0.97(1H,d,J=10.2Hz),1.12 and 1.23(each 3H,each s),1.52-2.46(14H,m),2.5 1(3H,s),4.26(1H,m),5.34-5.51(2H,m),6.23
(1H,d,J=8.4Hz),7.26 and 7.64 (each 2H,each d,J=8.4Hz).

IR(CHCl₃):3453,3027,3015,2925,2870,2665,1708,1648,1596,1516,1484 /cm.[α]_D=+67.7° (MeOH,c=0.82,22°C).

No.2a-148

[0256] [α]_D=+72.5° (MeOH,c=1.01,25°C).

No.2a-149

[0257] [α]_D=+67.8° (MeOH,c=0.98,25°C).

No.2a-150

[0258] CDCl₃ 300MHz

0.94(1H,d,J=10.2Hz),1.10 and 1.23(each 3H,each s),1.52-2.50(14H,m),4.2 2(1H,m),5.36-5.55(2H,m),6.48(1H,d,
J=8.4Hz),8.35(1H,s),8.90(1H,s).

IR(CHCl₃):3443,3374,3091,3024,3012,2925,2871,1709,1652,1525,1494 /cm. [α]_D=+58.1° (MeOH,c=1.01,23°C).

m.p.120.0-122.0°C

No.2a-151

[0259] [α]_D=+40.6° (MeOH,c=1.01,23°C).

No.2a-152

[0260] CDCl₃ 300MHz

0.96(1H,d,J=10.5Hz),1.10 and 1.24(each 3H, each s),1.50-2.50(14H,m),2.7 1(3H,s),4.26(1H,m),5.37-5.51(2H,m),6.02
(1H,d,J=9.0Hz),8.73(1H,s).

IR(CHCl₃):3463,3435,3087,3025,3014,2925,2870,1708,1649,1523,1503 /cm. [α]_D=+54.1° (MeOH,c=1.02,22°C).

No.2a-153

[0261] CDCl₃ 300MHz

0.95(1H,d,J=9.9Hz),1.11 and 1.23(each 3H,each s),1.50-2.50(14H,m),2.50(3H,s),4.26(1H,m),5.36-5.51(2H,m),6.01
(1H,d,J=8.4Hz),6.88(1H,d,J=5.1Hz), 7.26(1H,d,J=5.1Hz).

IR(CHCl₃):3469,3431,3025,3013,2925,2871,2664,1708,1639,1544,1505 /cm.[α]_D=+35.8° (MeOH,c=1.03,22°C).

No.2a-154

[0262] CDCl₃ 300MHz

0.95(1H,d,J=9.9Hz),1.10 and 1.22(each 3H,each s),1.52-2.46(14H,m),2.51(3H,d,J=1.2Hz),4.26(1H,m),5.34-5.50(2H,
m),6.00(1H,d,J=8.4Hz),6.73(1H,dd, J=5.1 and 3.6Hz),7.29(1H,d,J=3.6Hz).

IR(CHCl₃):3450,3431,3026,3011,2925,2869,1739,1708,1639,1547,1508 /cm.[α]_D=+50.5° (MeOH,c=1.01,22°C).

No.2a-155

[0263] CDCl₃ 300MHz

0.99(1H,d,J=10.2Hz),1.19 and 1.25(each 3H,each s),1.53-2.48(14H,m),4.3 1(1H,m),5.36-5.51(2H,m),6.79(1H,d,
J=9.3Hz),7.29(1H,m),7.41(1H,m),7.48(1 H,s),7.51(1H,m),7.66(1H,d,J=8.1Hz).

IR(CHCl₃):3436, 3029, 3024, 3015, 2925, 2871, 2670, 1708, 1659, 1598, 1510 /cm.[α]_D=+69.1° (MeOH,c=1.01,22°C).

No.2a.156

[0264] CDCl₃:CD₃O_D=10:1 300MHz

0.99(1H,d,J=9.9Hz),1.11 and 1.21(each 3H,each s),1.56-2.58(14H,m),4.22(1H,m),5.35-5.59(2H,m),6.83(1H.d,
1=8.4Hz),7.48(1H,d,J=8.4Hz),7.61(1H,dd, J=1.5 and 8.4Hz),8.09(1H,d,J=1.5Hz),8.12(1H,s).

IR(KBr):3422,3115,2985,2922,2869,2609,1708,1636,1578,1529,1470 /cm.

[α]_D=+62.8° (MeOH,c=1.01,22°C).

No.2a-157

[0265] [α]_D=+40.0° (MeOH,c=0.95,22°C).

No.2a-158

[0266] CDCl₃ 300MHz

1.00(1H,d,J=10.5Hz),1.17 and 1.24(each 3H,each s),1.54-2.50(14H,m),4.3 4(1H,m),5.36-5.52(2H,m),7.80(1H,d,
J=9.0Hz),9.30(1H,s).

IR(CHCl₃):3410,3122,3030,3012,2925,2871,2668,1709,1667,1538,1466 /cm.[α]_D=+44.9° (MeOH,c=0.99,22°C).

No.2a-159

[0267] CDCl₃ 300MHz

0.97(1H,d,J=10.2Hz),1.13 and 1.22(each 3H,each s),1.55-2.43(14H,m),3.0 3(6H,s),4.23(1H,m),5.32-5.51(2H,m),6.16
(1H,d,J=8.7Hz),6.87 and 7.63 (each 2H,each d,J=8.7Hz).

IR(CHCl₃):3457,3028,3006,2924,2870,2654,1739,1709,1637,1608,1608,1534, 1501 /cm.[α]_D=+64.8° (MeOH,c=1.01,22°C).

No.2a-160

[0268] d₆-DMSO 300MHz

0.83(1H,d,J=9.9Hz).1.02 and 1.19(each 3H,each s),1.38-1.61(3H,m),1.90-2. 32(11H,m),3.90(1H,m),5.41.5.44(2H,m),
7.32(1H,dd,J=0.9 and 7.2Hz),7.45. 7.60(2H,m),7.77(1H,dd,J=0.9 and 7.8Hz),8.03(1H,d,J=6.9Hz),12.40(1H,s).

IR(Nujol):3315,2924,2856,2656,2535,1737,1703,1637,1598,1581,1541 /cm.

[α]_D=+78.5° (MeOH,c=1.01,24°C).

m.p.161.0-162.0°C

No.2a-161

[0269] [α]_D=+65.3° (MeOH,c=1.00,22°C).

No.2a-162

[0270] CDCl₃ 300MHz

0.99(1H,d,J=10.2Hz),1.13 and 1.25(each 3H,each s),1.53-2.45(14H,m),4.3 0(1H,m),5.36-5.51(2H,m),6.32(1H,d,
J=8.4Hz),7.88 and 8.28(each 2H,each d, J=9.0Hz) .

IR(CHCl₃):3448,3029,3016,2925,2870,1708,1664,1602,1527,1484,1347 /cm.[α]_D=+72.7° (MeOH,c=1.02,22°C).

[0271] No.2a-163

[0272] CDCl₃ 300MHz.

EP 0 837 052 B1

0.96(1H,d,J=10.2Hz), 1.11 and 1.23(each 3H,each s), 1.55-2.51(14H,m), 4.2 6(1H,m), 5.36-5.57(2H,m), 6.68(1H,d, J=7.8Hz), 7.41(1H,dd,J=4.8 and 8.1Hz), 8.20(1H,d,J=8.1Hz), 8.66(1H,d,J=4.8Hz), 9.00(1H,s).
IR(CHCl₃): 3448, 3026, 3013, 2925, 2870, 2534, 1709, 1658, 1590, 1515, 1471 /cm.
[α]_D=+71.3° (MeOH, c=1.01, 22°C).

5

No.2a-164

[0273] [α]_D=+40.8° (MeOH, c=0.98, 22°C).

[0274] No.2a-165

10

CDCl₃ 300MHz

0.96(1H,d,J=10.5Hz), 1.11 and 1.24(each 3H, each s), 1.55-2.52(14H,m), 4.2 4(1H,m), 5.37-5.57(2H,m), 6.63(1H, d,J=7.8Hz), 7.59 and 8.63(each 2H each d,J=6.0Hz).

IR(CHCl₃): 3447, 3346, 3028, 3016, 2925, 2870, 2538, 1941, 1708, 1662, 1556, 1516 /cm.

[α]_D=+75.4° (MeOH, c=1.01, 22°C).

15

[0275] No.2a-166

CDCl₃ 300MHz

0.97(1H,d,J=10.2Hz), 1.11 and 1.22(each 3H,each s), 1.51-2.44(14H,m), 2.9 5(6H,s), 4.25(1H,m), 5.33-5.50(2H,m), 6.19 (1H,d,J=8.7Hz), 6.77 and 6.97 (each 2H, each d,J=8.4Hz), 6.94 and 7.65(each 2H,each d,J=9.0Hz).

IR(CHCl₃): 3453, 3024, 3016, 2924, 2871, 2806, 1739, 1708, 1647, 1612, 1604, 1515, 1490 /cm.

20

[α]_D=+53.1° (MeOH, c=1.02, 23°C).

m.p. 104.0-105.5°C

No.2a-167

25

[0276] CDCl₃ 300MHz

1.01(1H,d,J=9.9Hz), 1.19 and 1.26(each 3H,each s), 1.56-2.53(14H,m), 4.37(1H,m), 5.35-5.55(2H,m), 6.47(1H,d, J=8.4Hz), 7.61-7.71(2H,m), 7.79(2H,s), 7.89-7.97(2H,m), 8.27(1H,d,J=2.1Hz), 8.66-8.73(2H,m).

IR(CHCl₃): 3450, 3024, 3014, 2925, 2870, 2667, 1707, 1650, 1531, 1509 /cm.

[α]_D=+70.5° (MeOH, c=1.00, 22°C).

30

No.2a-168

[0277] CDCl₃ 300MHz

1.02(1H,d,J=10.2Hz), 1.20 and 1.26(each 3H,each s), 1.56-2.50(14H,m), 4.3 8(1H,m), 5.36-5.56(2H,m), 6.51(1H,d, J=8.9Hz), 7.61-7.93(7H,m), 8.74(1H,d,J=8.4Hz), 9.15(1H,s).

35

IR(CHCl₃): 3517, 3451, 3060, 3028, 3011, 2925, 2870, 2664, 1709, 1651, 1519, 1498 /cm.

[α]_D=+54.4° (MeOH, c=1.00, 23°C).

No.2a-169

40

[0278] CDCl₃ 300MHz

0.96(1H,d,J=10.5Hz), 1.09 and 1.21(each 3H,each s), 1.50-2.44(14H,m), 3.8 5(3H,s), 4.24(1H,m), 5.32-5.48(2H,m), 6.19 (1H,d,J=8.4Hz), 6.94 and 7.45 (each 2H,each d,J=9.0Hz), 7.11 and 7.45(each 2H,each d,J=8.7Hz).

IR(CHCl₃): 3516, 3453, 3029, 3009, 2925, 2870, 2840, 2665, 1708, 1650, 1593, 1515, 1493, 1482 /cm.

45

[α]_D=+57.8° (MeOH, c=1.00, 23°C).

No.2a-170

[0279] CDCl₃ 300MHz

50

0.98(1H,d,J=10.2Hz), 1.15 and 1.24(each 3H,each s), 1.52-2.50(14H,m), 4.2 8(1H,m), 5.33-5.54(2H,m), 6.25(1H,d, J=8.2Hz), 7.38-7.44(2H,m), 7.74(1H,s), 7.81-7.86(2H,m).

IR(CHCl₃): 3517, 3448, 3427, 3024, 3013, 2925, 2870, 2669, 1708, 1650, 1562, 1535, 1500 /cm.

[α]_D=+61.6° (MeOH, c=1.00, 23°C).

55

No.2a-171

[0280] CDCl₃ 300MHz

0.96(1H,d,J=10.2Hz), 1.11 and 1.22(each 3H,each s), 1.52-2.42(14H,m), 2.48 (3H,s), 4.21(1H,m), 5.31-5.52(2H,m), 6.06

EP 0 837 052 B1

(1H,d,J=8.2Hz), 6.97 and 7.59 (each 1H,each d,J=1.2Hz).
 IR(CHCl₃):3452,3113,3028,3007,2925,2870,2669,1708,1645,1554,1509 /cm.
 [α]_D=+52.4° (MeOH,c=1.00,23°C).

5 No.2a-172

[0281] CDCl₃ 300MHz
 0.96(1H,d,J=10.2Hz),1.09 and 1.28(each 3H,each s),1.50-2.40(14H,m),2.6 9(3H,s),4.24(1H,m),5.35-5.51(2H,m),5.96
 (1H,d,J=8.7Hz),7.03 and 7.07 (each 1H,each d,J=5.4Hz).
 10 IR(CHCl₃):3451,3031,3013,2925,2870,2666,1708,1647,1542,1497 /cm.
 [α]_D=+51.2° (MeOH,c=1.00,23°C).

No.2a-173

15 [0282] CDCl₃ 300MHz
 0.95(1H,d,J=10.2Hz),1.10 and 1.23(each 3H,each s),1.50-2.45(14H,m),4.2 2(1H,m),5.35-5.49(2H,m),6.05(1H,d,
 J=8.4Hz),7.26 and 7.75(each 1H,each d,J=1.5Hz).
 IR(CHCl₃):3451,3011,3029,3011,2925,2870,1708,1652,1538,1500 /cm.
 [α]_D=+50.6° (MeOH,c=1.01,23°C).

20

No.2a-174

[0283] CDCl₃ 300MHz
 0.96(1H,d,J=10.2Hz),1.13 and 1.23(each 3H,each s),1.52-2.50(14H,m),4.2 9(1H,m),5.35-5.51(2H,m),7.02(1H,d,
 25 J=8.4Hz),7.32 and 8.16(each 1H,each d,J=3.9Hz).
 IR(CHCl₃):3417,3115,3023,3014,2925,2870,1708,1645,1530 /cm.
 [α]_D=+48.8° (MeOH,c=1.02,23°C).

No.2a-175

30

[0284] CDCl₃ 300MHz
 0.97(1H,d,J=10.2Hz),1.14 and 1.23(each 3H,each s),1.50-2.52(14H,m),2.5 2(3H,s),4.29(1H,m),5.34-5.51(2H,m),7.78
 (1H,d,J=9.0Hz),7.24 and 7.52 (each 1H,each d,J=5.4Hz).
 IR(CHCl₃):3329,3093,3023,3015,2924,2871,1708,1640,1526 /cm. [α]_D=+45.0° (MeOH,c=1.01,23°C).

35

No.2a-176

[0285] CDCl₃ 300MHz
 0.95(1H,d,J=10.5Hz),1.09 and 1.23(each 3H,each s),1.52-2.46(14H,m),2.4 0(3H,d,J=0.9Hz),4.24(1H,m),5.35-5.51(2H,
 40 m),6.05(1H,d,J=8.7Hz),6.95(1H, m),7.57(1H,d,J=3.3Hz).
 IR(CHCl₃):3517,3444,3103,3024,3013,2926,2870,1739,1748,1649,1636,15071 cm.
 [α]_D=+54.8° (MeOH,c=1.01,23°C).
 m.p.97.0-99.0°C

45 No.2a-177

[0286] CDCl₃ 300MHz
 0.97(1H,d,J=10.2Hz), 1.11 and 1.23(each 3H,each s), 1.52-2.45(14H,m), 3.9 3(3H,s), 4.27(1H,m), 5.34-5.50(2H,m),
 6.35(1H,d,J=3.3Hz), 7.80(1H,d,J=8.7Hz), 8.10(1H,d,J=3.3Hz).
 50 IR(CHCl₃):3395,3121,3031,3019,3012,2925,2871,1739,1709,1640,1557,1533 /cm.
 [α]_D=+22.8° (MeOH,c=1.01,23°C).
 m.p.109.0-112.0°C

No.2a-178

55

[0287] CDCl₃ 300MHz
 0.96(1H,d,J=10.5Hz),1.10 and 1.23(each 3H,each s), 1.51-2.45(14H, m),4.2 4(1H,m),5.35-5.50(2H,m),6.09(1H,d,
 J=8.4Hz),7.17-7.31(6H,m),7.95(1H,d,J= 1.5Hz).

EP 0 837 052 B1

IR(CHCl₃):3510,3451,3062,3031,3022,3011,2925,2870,2662,1708,1651,1582, 1535,1497,1477/cm.
[α]_D=+47.9° (MeOH,c=1.01,25°C).

No.2a-179

5

[0288] CDCl₃ 300MHz
0.96(1H,d,J=10.2Hz),1.14 and 1.24(each 3H,each s),1.52-2.48(14H,m),4.3 0(1H,m),5.36-5.52(2H,m),6.73(1H,d,
J=9.0Hz),6.26 and 7.37(each 1H,each d,J=6.0Hz).

IR(CHCl₃):3509,3429,3115,3094,3025,3014,2925,2871,2666,1708,1649,1529, 1510 /cm.

10

[α]_D=+51.0° (MeOH,c=1.02,25°C).

No.2a-180

[0289] CDCl₃ 300MHz

15

0.95(1H,d,J=10.2Hz),1.14 and 1.24(each 3H,each s),1.52-2.46(14H,m),3.8 9(3H,s),4.21(1H,m),5.35-5.50(2H,m),6.05
(1H,d,J=8.4Hz),6.46 and 7.04 (each 1H,each d,J=1.8Hz).

IR(CHCl₃):3516,3450,3114,3031,3010,2925,2871,1708,1648,1546,1511,1477 /cm.

[α]_D=+49.1° (MeOH,c=1.01,25°C).

20

No.2a-181

[0290] CDCl₃ 300MHz

0.97(1H,d,J=10.2Hz),1.14 and 1.23(each 3H,each s),1.52-2.48(14H,m),2.4 2(3H,s),4.31(1H,m),5.34-5.52(2H,m),8.07
(1H,d,J=9.3Hz),7.27 and 8.17 (each 1H,each d,J=3.3Hz).

25

IR(CHCl₃):3510,3301,3112,3023,3007,2924,2871,2663,1708,1636,1534 /cm.

[α]_D=+41.0° (MeOH,c=0.96,25°C).

No.2a-182

30

[0291] CDCl₃ 300MHz

0.96(1H,d,J=10.2Hz),1.11 and 1.23(each 3H,each s),1.53-2.46(14H,m),2.5 1(3H,s),4.21(1H,m),5.35-5.51(2H,m),6.05
(1H,d,J=8.1Hz),7.26 and 7.78 (each 1H,each d,J=1.8Hz).

IR(CHCl₃):3509,3450,3109,3024,3012,2925,2870,2666,1708,1650,1535,1 498,1471 /cm.

[α]_D=+52.9° (MeOH,c=0.95,25°C).

35

No.2a-183

[0292] CDCl₃ 300MHz

40

0.96(1H,d,J=10.5Hz),1.12 and 1.22(each 3H,each s),1.52-2.46(14H,m),4.2 5(1H,m),5.33-5.51(2H,m),6.17(1H,d,
J=8.7Hz),7.01-7.05(3H,m),7.14 and 7.6 2(each 2H,each d,J=8.7Hz),7.27-7.34(2H,m).

IR(CHCl₃):3428,3026,3015,2925,2870,2666,1739,1708,1643,1613,1594,1526, 1499 /cm.

[α]_D=+64.8° (MeOH,c=1.02,23°C).

No.2a-184

45

[0293] CDCl₃ 300MHz

1.01(1H,d,J=10.2Hz),1.18 and 1.26(each 3H,each s), 1.55-2.50(14H,m),4.3 5(1H,m),5.35-5.55(2H,m),6.42(1H,d,
J=8.7Hz),7.46-7.52(2H, m),7.73(1H, dd,J =1.8 and 8.4Hz),7.83-7.89(2H,m),8.21(1H,m),8.59(1H,d,J=1.5Hz).

IR(CHCl₃):3451,3031,3014,2925,2870,2660,1739,1708,1650,1604,1513,1463 /cm.

50

[α]_D=+58.3° (MeOH,c=1.00,23°C).

No.2a-185

[0294] CDCl₃ 300MHz

55

1.00(1H,d,J=10.2Hz),1.18 and 1.25(each 3H,each s),1.55-2.50(14H,m),4.3 4(1H,m),5.35-5.54(2H,m),6.36(1H,d,
J=8.7Hz),7.37(1H,t,J=7.4Hz),7.50(1H,m),7.57-7.59(2H,m),7.79(1H,dd,J=1.8 and 8.1Hz),7.99(1H,d,J=7.8Hz),8.39(1
H,d,J=1.8Hz).

IR(CHCl₃):3451,3030,3020,2870,2665,1708,1652,1632,1603,1586,1514,1469, 1448 /cm.

EP 0 837 052 B1

$[\alpha]_D = +59.4^\circ$ (MeOH, c=1.01, 24°C).

No.2a-186

5 **[0295]** CDCl₃ 300MHz
1.00(1H,d,J=10.5Hz), 1.17 and 1.25(each 3H,each s), 1.54-9.50(14H,m), 4.3 3(1H,m), 5.35-5.54(2H,m), 6.37(1H,d, J=8.7Hz), 7.37(1H,t,J=7.4Hz), 7.51(1H,t, J=7.8Hz), 7.56(1H,m), 7.70(1H.dd,J=1.2 and 8.4Hz), 7.97(3H,m).
IR(CHCl₃): 3451, 3030, 3014, 2924, 2870, 2671, 1739, 1708, 1652, 1577, 1517, 1488, 1471 /cm.
[α]_D=+72.2° (MeOH, c=1.00, 24°C).

10 No.2a-187

[0296] CDCl₃ 300MHz
1.00(1H,d,J=9.8Hz), 1.18 and 1.25(each 3H,each s), 1.54-2.53(14H,m), 4.07 3H,s), 4.37(1H,m), 5.30-5.54(2H,m), 7.34
15 (1H,m), 7.47(1H,s), 7.47-7.60(2H,m), 7.93(1H,d,J=7.8Hz), 8.43(1H,s), 8.49(1H,d,J=9.0Hz).
IR(CHCl₃): 3397, 3074, 3027, 3020, 3009, 2924, 1738, 1708, 1647, 1533, 1534, 1465, 1453 /cm.
[α]_D=+43.7° (MeOH, c=1.01, 25°C).

No.2a-188

20 **[0297]** CDCl₃ 300MHz
0.97(1H,d,J=10.2Hz), 1.11 and 1.23(each 3H,each s), 1.53-2.50(14H,m), 4.2 3(1H,m), 5.37-5.50(2H,m), 8.10(1H,d, J=9.0Hz), 6.20(1H,m), 6.51(1H,m), 6.97(1 H,m), 10.81(1H,brs).
IR(CHCl₃): 3450, 3236, 3112, 3029, 3015, 2925, 2871, 2645, 1701, 1616, 1558, 1516 /cm.
25 [α]_D=+50.6° (MeOH, c=1.01, 24°C).

No.2a-189

[0298] CDCl₃ 300MHz
30 0.94(1H,d,J=9.9Hz), 1.11 and 1.23(each 3H,each s), 1.50-2.46(14H,m), 3.93(3H,s), 4.18(1H,m), 5.35-5.52(2H,m), 6.03 (1H,d,J=9.3Hz), 6.09(1H,m), -6.48(1H, m), 6.73(1H,m).
IR(CHCl₃): 3452, 3102, 3028, 3007, 2925, 2871, 2666, 1739, 1708, 1650, 1536, 1499, 1471 /cm.
[α]_D=+49.8° (MeOH, c=1.01, 23°C).
m.p. 101.5-103.5°C

35 No.2a-190

[0299] CDCl₃ 300MHz
40 0.94(1H,d,J=10.2Hz), 1.11 and 1.21(each 3H,each s), 1.54-2.47(14H,m), 4.2 3(1H,m), 5.33-5.52(2H,m), 6.06(1H,d, J=9.0Hz), 6.34(1H,m), 6.75(1H,m), 6.36(1 H,m), 9.71(1H,brs).
IR(CHCl₃): 3470, 3215, 3030, 3020, 3010, 2925, 2871, 2664, 1709, 1613, 1564, 1510/cm.
[α]_D=+43.3° (MeOH, c=1.01, 24°C).

No.2a-191

45 **[0300]** CDCl₃ 300MHz
0.96(1H,d,J=10.2Hz), 1.11 and 1.22(each 3H,each s), 1.55-2.44(14H,m), 3.6 6(3H,s), 4.20(1H,m), 5.35-5.51(2H,m), 5.93 (1H,d,J=8.4Hz), 6.27(1H,dd,J=1.8 and 2.7Hz), 6.56(1H,t,J=2.7Hz), 7.19(1H,t,J=1.8Hz).
IR(CHCl₃): 3452, 3031, 3018, 3006, 2925, 2871, 2662, 1736, 1710, 1634, 1609, 1556, 1498 /cm.
50 [α]_D=+43.1° (MeOH, c=1.01, 23°C).

No.2a-192

[0301] CDCl₃ 300MHz
55 0.96(1H,d,J=10.5Hz), 1.11 and 1.21(each 3H,each s), 1.43(3H,t,J=7.5Hz), 1.54-2.44(14H,m), 3.93(2H,q,J=7.5Hz), 4.21 (1H,m), 5.33-5.51(2H,m), 5.94(1H,d, J=8.4Hz), 6.27(1H,dd,J=1.8 and 2.7Hz), 6.62(1H,t,J=2.7Hz), 7.26(1H,t,J=1.8 Hz).
IR(CHCl₃): 3630, 3452, 3032, 3018, 3006, 2925, 2871, 2661, 1735, 1710, 1633, 1610, 1555, 1497 /cm.
[α]_D=+40.1° (MeOH, c=1.00, 23°C).

No.2a-193

[0302] CDCl₃ 300MHz

0.95(1H,d,J=10.2Hz), 1.10 and 1.22(each 3H,each s), 1.53-2.49(14H,m), 2.5 8(3H,s), 4.21(1H,m), 5.35-5.54(2H,m),
 6.15(1H,d,J=8.1Hz), 6.52(1H,dd,J=1.8 and 3.6Hz), 7.29(1H,t,J=3.6Hz), 7.94(1H,t,J=1.8Hz).

IR(CHCl₃):3516,3450,3410,3152,3027,3015,2925,2871,2670,1732,1648,1574, 1509 /cm.

[α]_D=+45.0° (MeOH,c=1.01,25°C).

No.2a-194

[0303] CDCl₃ 300MHz

0.99(1H,d,J=10.2Hz),1.11 and 1.24(each 3H,each s),1.52-2.53(14H,m),4.3 4(1H,m),5.33-5.57(2H,m),6.21(1H,d,
 J=8.6Hz),7.35-7.50(2H,m),7.83(1H,s),7. 86(1H,m),.8.31 (1H,m).

IR(CHCl₃):3443,3067,3013,2925,2870,2665,1708,1651,1515,1493 /cm.

[α]_D=+55.7° (MeOH,c=1.01,23°C).

No.2a-195

[0304] CDCl₃ 300MHz

1.01(1H,d,J=10.0Hz),1.06 and 1.26(each 3H,each s),1.50-2.64(14H,m),2.6 8(3H,s),4.40(1H,m),5.36-5.61(2H,m),6.02
 (1H,d,J=9.4Hz),7.30-7.42(2H,m),7. 73-7.86(2H,m).

IR(CHCl₃):3510,3434.3062,3029,3014,2924,2871,2669,1708,1650,1563.1539, 1500 /cm.

[α]_D=+72.4° (MeOH,c=1.00,23°C).

m.p.111.0-112.0°C

No.2a-196

[0305] CDCl₃ 300MHz

0.42 and 1.04(each 3H,each s),0.80(1H,d,J=10.0Hz),1.11-2.48(14H,m),2.2 4(3H,s),4.02(1H,m),5.23-5.44(2H,m),5.53
 (1H,d,J=8.8Hz),7.27-7.31(2H,m),7. 42-7.48(3H,m),7.93(1H,s).

IR(CHCl₃):3419,3114,3025,3006,2924,2871,2662,1737,1709,1636,1540,1519 /cm.

[α]_D=+43.7° (MeOH,c=1.01,23°C).

No.2a-197

[0306] CDCl₃ 300MHz

0.95(1H,d,J=10.0Hz), 1.09 and 1.23(each 3H,each s), 1.54-2.46(18H,m), 2.7 7(4H,brs), 4.21(1H,m), 5.32-5.54(2H,m),
 6.02(1H,d,J=8.6Hz), 7.43(1H,s).

IR(CHCl₃):3445,3101,3024,3014,2928,2865,2661,1739,1708 1646,1550,1507 /cm.

[α]_D=+51.9° (MeOH,c=1.01,23°C).

No.2a-198

[0307] CDCl₃ 300MHz

0.96(1H,d,J=10.2Hz),1.11 and 1.22(each 3H,each s),1.50-2.44(14H,m),4.2 4(1H,m),4.42(2H,s),5.35-5.49(2H,m),6.25
 (1H,d,J=8.1Hz),7.33(1H,m),7.43(1 H,dd,J=1.5and 7.5Hz),7.49(1H,d,J=8.1Hz),7.60-7.63(1H,m),7.68(1H,dd,J=1. 8 and
 7.8Hz),8.02(1H,d,J=1.8Hz),8.19(1H,dd,J=1.5 and 8.1Hz).

IR(CHCl₃):3448,3030,3012,2925,2870,1739,1708,1671,1588,1559,1514,1472 /cm.

[α]_D=+56.9° (MeOH,c=1.01,24°C).

No.2a-199

[0308] CDCl₃ 300MHz

0.96(1H,d,J=10.2Hz),1.11 and 1.22(each 3H,each s),1.51-2.46(14H,m),3.4 0(1H,m),3.76(1H,m),4.24(1H,m),5.33-5.51
 (3H,m),6.25(1H,m),7.16(1H,m),7.2 4-7.33(2H,m),7.46(1H,d,J=7.5Hz),7.52-7.60(2H,m),7.85(1H,dd,J=1.8 and 4. 5Hz):

IR(CHCl₃):3583,3447,3062,3028,3013,2924,2871,2663,1708,1651,1600,1557, 1514,1471 /cm.

[α]_D=+54.8° (MeOH,c=1.00,23°C).

No.2a-200

[0309] CDCl₃ 300MHz

5 0.96(1H,d,J=10.2Hz),1.12 and 1.23(each 3H,each s),1.51-2.46(14H,m),4.2 5(1H,m),5.34-5.51(2H,m),6.25(1H,d,J=8.4Hz),7.02 and 7.10(each,1H,each d,J=12.3Hz),7.23-7.33(4H,m),7.50(1H,m),7.64(1H,dd,J=1.8 and 7.8Hz),7.8 2(1H,d,J=1.8Hz).

IR(CHCl₃):3450,3060,3025,3014,2925,2871,2662,1708,1653,1596,1542,1513, 1473 /cm.[α]_D=+62.5° (MeOH,c=1.00,24°C).

10 No.2a-201

[0310] CDCl₃ 300MHz

0.95(1H,d,J=9.9Hz),1.15 and 1.22(each 3H,each s),1.55-2.60(14H,m),4.26(1H,m),5.35-5.63(2H,m),7.14(1H,d,J=9.9Hz),7.34 and 7.40(each,1H,each d,J=12.9Hz),7.62-7.73(4H,m),8.25-8.30(2H,m),8.72(1H,d,J=1.5Hz).

15 IR(CHCl₃):3443,3389,3297,3061,3030,3016,2925 2870,1726,1708 1652,160 3;1521,1483,1472,1309 /cm.

[α]_D=+61.1° (MeOH,c=1.01,23°C).

No.2a-202

20 [0311] CDCl₃ 300MHz

0.96(1H,d,J=10.2Hz),1.09 and 1.22(each 3H,each s),1.52-2.43(14H,m),2.6 3(3H,s),4.25(1H,m),5.33-5.49(2H,m),6.19(1H,d,J=8.4Hz),7.10 and 7.58 (each, 2H,each d,J=9.0Hz),7.21(1H,m),7.30-7.32(2H,m),7.46(1H,d,J=7.5Hz)

IR(CHCl₃):3511,3453,3062,3032,3014,2925 2870,1739,1708,1650,1595,1556, 1516,1482,1471 /cm.[α]_D=+60.2° (MeOH, c=1.01,25°C).

25

No.2a-203

[0312] CDCl₃ 300MHz

30 0.96(1H,d,J=10.5Hz),1.09 and 1.23(each 3H,each s), 1.52-2.43(14H,m),4.2 3(1H,m),5.35-5.51(2H,m),5.93(1H,d,J=8.7Hz),6.56(1H,dd,J=0.9 and 1.8Hz), 7.43(1H,t,J=1.8Hz),7.92(1H,dd,J=0.9 and 1.8Hz).

IR(CHCl₃):3517,3450,3134,3031,3008,2925,2870,2667,1708,1656,1588,1570, 1514 /cm.[α]_D=+46.7° (MeOH,c=0.92,25°C).

No.2b-1

35

[0313] [α]_D= +25.6° (MeOH,c=1.01,23°C).

No.2b-2

40

[0314] [α]_D= +38.9° (MeOH,c=1.01,24°C).

No.2c-1

[0315] [α]_D= +60.5° (MeOH,c=1.01,22°C).

45

No.2c-2

[0316] [α]_D= +55.8° (MeOH,c=0.92,22°C).

50

No.2c-3

[0317] [α]_D= +54.7° (MeOH,c=1.01,22°C).

No.2d-1

55

[0318] [α]_D= -6.2° (MeOH,c=1.00,21°C).

No.2d-2

[0319] $[\alpha]_D = +15.8^\circ$ (MeOH, c=0.34, 22°C).

5 No.2d-3

[0320] $[\alpha]_D = +31.6^\circ$ (MeOH, c=1.01, 22°C).

No.2e-1

10

[0321] $[\alpha]_D = -9.4^\circ$ (MeOH, c=1.00, 22°C).

No.2e.2

15

[0322] $[\alpha]_D = -1.8^\circ$ (MeOH, c=1.02, 23°C).

No.2e-3

[0323] $[\alpha]_D = -6.7^\circ$ (MeOH, c=1.01, 23°C).

20

No.2f-1

[0324] $[\alpha]_D = +6.8^\circ$ (MeOH, c=1.01, 23°C).

25

No.2f-2

[0325] $[\alpha]_D = -2.6^\circ$ (MeOH, c=1.00, 22°C).

No.2f-3

30

[0326] $[\alpha]_D = -3.5^\circ$ (MeOH, c=1.01, 22°C).

No.2g-1

35

[0327] $[\alpha]_D = +54.6^\circ$ (MeOH, c=1.01, 24°C).

[0328] Compounds prepared in Examples above were tested for in vivo and in vitro activity according to the method shown in Experimental examples below.

Experiment 1 Binding to PGD₂ Receptor

40

Material and Method

(1) Preparation of Human Platelet Membrane Fraction

45

[0329] A Blood sample was obtained using a plastic syringe containing 3.8 % sodium citrate from veins of healthy volunteers (adult male and female), put into a plastic test tube and mixed gently by inversion. The sample was then centrifuged at 1800 rpm, 10 min at room temperature, and supernatant containing PRP (platelet rich plasma) was collected. The PRP was re-centrifuged at 2300 rpm, 22 min at room temperature to obtain platelets. The platelets were homogenized using a homogenizer (Ultra-Turrax) followed by centrifugation 3 times at 20,000 rpm, 10 min at 4°C to obtain a platelet membrane fraction. After protein determination, the membrane fraction was adjusted to 2 mg/ml and preserved in a refrigerator at -80°C until use.

50

(2) Binding to PGD₂ Receptor

55

[0330] To a binding-reaction solution (50 mM Tris/HCl, pH 7.4, 5 mM MgCl₂) (0.2 ml) were added human platelet membrane fraction (0.1 mg) and 5 nM [³H]PGD₂ (115Ci/mmol), and reacted at 4°C for 90 min. After the reaction finished, the reaction mixture was filtered through a glass fiber filter paper, washed several times with cooled saline, and measurement made of radioactivity retained on the filter paper. The specific binding was calculated by subtracting the non-

specific binding (the binding in the presence of 10 μM PGD_2) from the total binding. The binding-inhibitory activity of each compound was expressed as concentration required for 50 % inhibition (IC_{50}), which was determined by depicting a substitution curve by plotting the binding ratio (%) in the presence of each compound, where the binding ratio in the absence of a test compound is - 100 %. The results are shown in Table below.

Compound number	Activity (μM)	compound number	activity (μM)
2a-4		0.54	
2a-17		0.12	
2a-21		5.2	
2a-28		0.046	
2a-95		1.6	
2a-109		0.003	

Experiment 2 Evaluation of Antagonistic Activity Against PGD_2 Receptor Using Human Platelet

[0331] Peripheral blood was obtained from a healthy volunteer using a syringe in which 1/9 volume of citric acid/dextrose solution had been previously added. The syringe was subjected to centrifugation at 180 g for 10 min to obtain the supernatant (PRP: platelet rich plasma). The resultant RRP was washed 3 times with a washing buffer and the number of platelets was counted with a micro cell counter. A suspension adjusted to contain platelets at a final concentration of $5 \times 10^8/\text{ml}$ was warmed at 37°C , and then subjected to the pretreatment with 3-isobutyl-1-methylxanthine (0.5mM) for 5 min. To the suspension was added a test compound diluted at various concentrations. Ten-minutes later, the reaction was induced by the addition of 0.1-2.0 μM PGD_2 and, 15-minutes later, stopped by the addition of HC1. The platelets were destroyed with an ultrasonic homogenizer. After centrifugation, the cAMP in the supernatant was determined by radioassay. PGD_2 receptor antagonism of a drug was evaluated as follows. The inhibition rate regarding cAMP increased by the addition of PGD_2 was determined at individual concentration, and then the concentration of the drug required for 50 % inhibition (IC_{50}) was calculated. The results are shown in the Table below.

Compound number	Inhibition of Increase of Human Platelet cAMP (IC_{50})(μM)
2a-2	0.77
2a-4	0.49
2a-35	1.52
2a-75	0.71

Experiment 3 Experiment Using Nasal Occlusion Model


[0332] The method used for measuring the nasal cavity resistance and evaluating the anti-nasal occlusion using a guinea pig are described below.


[0333] A 1% ovalbumin (OVA) solution was treated with an ultrasonic nebulizer to obtain an aerosol. A Hartley male guinea pig was sensitized by inhaling twice the aerosol for 10 min at one-week intervals. Seven-days after the sensitization, the guinea pig was exposed to an antigen to initiate the reaction. Then the trachea was incised under anesthesia with pentobarbital (30 mg/kg, i.p.) and cannulas were inserted into the trachea at the pulmonary and nasal cavity sides. The canal inserted at the pulmonary side was connected with an artificial respirator that provides 4 ml air 60 times/min. After arresting the spontaneous respiration of a guinea pig with Garamin (2 mg/kg, i.v.), air was supplied to the snout side with an artificial respirator at the frequency of 70 times/min, and the flow rate of 4 ml air/time, and the atmospheric pressure required for the aeration was measured by the use of a transducer fitted at the branch. The measurement was used as a parameter of the nasal cavity resistance. The exposure of an antigen was carried out by generating aerosol of 3 % OVA solution for 3 min between the respirator and nasal cavity cannula. The test drug was injected intravenously 10 min before the antigen exposure. The nasal resistance between 0 to 30 min was measured continuously and the effect was expressed as inhibition rate to that obtained for vehicle using the AUC for 30 min (on the vertical axis, nasal cavity resistance ($\text{cm H}_2\text{O}$), and on the horizontal axis, time (0 - 30 min)) as an indication. The result is shown below.

Compound number	Inhibition Rate (%) 1 mg/kg (i.v.)	Remarks
2a-4	60	
2a-21	52	

Formulation 1 Preparation of Tablets

Claims

$$\begin{array}{c} \text{A-R} \\ | \\ \text{Y} \\ | \\ \text{N-CO-X}_1\text{-X}_2\text{-X}_3 \\ | \\ \text{R} \end{array} \quad (\text{Ib})$$




X₃ is alkyl, alkenyl, alkynyl, aryl, aralkyl, heterocyclic group, cycloalkyl, cycloalkenyl, thiazolinyldenemethyl,

thiazolidinylidenemethyl, $-\text{CH}=\text{NR}_6$ or $-\text{N}=\text{C}(\text{R}_7)\text{R}_8$;

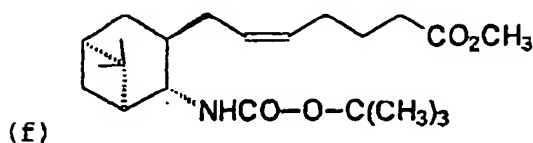
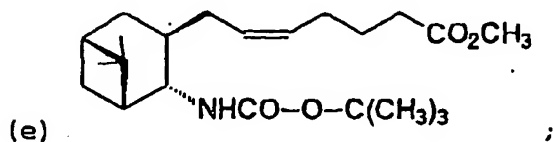
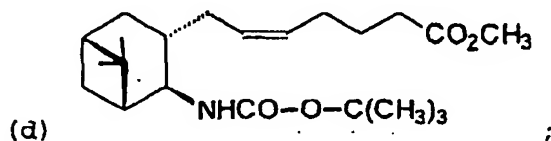
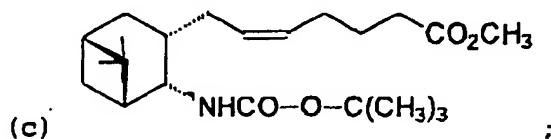
R_5 , R_{51} , R_{52} , R_{53} , R_{54} , R_{55} and R_{56} , each are hydrogen or alkyl;

R_6 is hydrogen, alkyl, hydroxy, alkoxy, carbamoyloxy, thiocarbamoyloxy, ureido or thioureido;

R_7 and R_8 each are independently alkyl, alkoxy or aryl;

and n is 1 or 2;

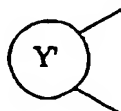
wherein a cyclic substituent may have one to three substituents selected from the group consisting of nitro, alkoxy, sulfamoyl, substituted- or unsubstituted-amino, acyl, acyloxy, hydroxy, halogen, alkyl, alkynyl, carboxy, alkoxycarbonyl, aralkoxycarbonyl, aryloxycarbonyl, mesyloxy, cyano, alkenyloxy, hydroxyalkyl, trifluoromethyl, alkylthio, $-\text{N}=\text{PPh}_3$, oxo, thioxo, hydroxyimino, alkoxyimino, phenyl and alkylenedioxy, or its salt or hydrate thereof; with the proviso that compounds (a) wherein X_1 and X_2 are a single bond, and X_3 is phenyl; (b) wherein X_1 is a single bond, X_2 is $-\text{O}-$, and X_3 is benzyl;



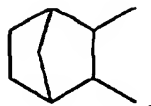
and

are excluded.

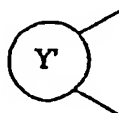
2. The compound of claim 1, a salt or hydrate thereof, wherein



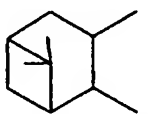
is



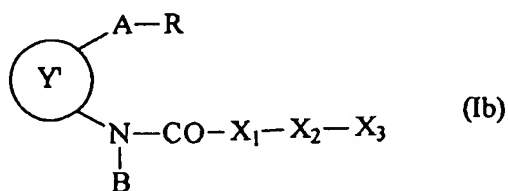
3. The compound of claim 2, a salt or hydrate thereof, wherein R is COOR₁.
4. The compound of claim 2, salt or hydrate thereof, wherein X₁ is phenylene or thiophenediyl, X₂ is a single bond, -N=N-, -CH=CH-, ethynylene, -O-, -S-, -CO-, -CON(R₅₅)-, -N(R₅₁)CO- and X₃ is phenyl or thienyl.
5. The compound of claim 1, a salt or hydrate thereof, wherein



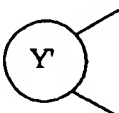
is



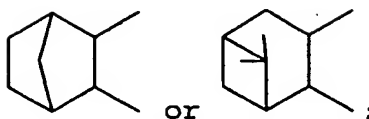
6. The compound of claim 5, a salt or hydrate thereof, wherein B is hydrogen, both X₁ and X₂ are a single bond, X₃ is thienyl, thiazolyl, thiadiazolyl, isothiazolyl, pyrrolyl, pyridyl, benzofuryl, benzimidazolyl, benzothienyl, dibenzofuryl, dibenzothienyl, quinolyl or indolyl.
7. The compound of claim 5, a salt or hydrate thereof, wherein X₁ is phenylene, thiophenediyl, indolediyl or oxazolediyl, X₂ is a single bond, -N=N-, -CH=CH-, ethynylene, -S- or -O-, and X₃ is aryl or heterocyclic group.
8. A compound of the formula (Ib) below, for use in a method of treating diseases in which mast cell dysfunction is involved, tracheal contraction, asthma, allergic rhinitis, allergic conjunctivitis, urticaria, injury due to ischemic reperfusion, nasal occlusion and inflammation:



wherein



is



wherein A is alkylene which optionally is intervened by hetero atom or phenylene, contains oxo group, and/or has an unsaturated bond;

B is hydrogen, alkyl, aralkyl or acyl;

R is COOR₁, CH₂OR₂ or CON(R₃)R₄;

R₁ is hydrogen or alkyl;

R₂ is hydrogen or alkyl;

R₃ and R₄ each are independently hydrogen, alkyl, hydroxy or alkylsulfonyl;

X₁ is a single bond, phenylene, naphthylene, thiophenediyl, indole-diyl, or oxazole-diyl;

X₂ is a single bond, -N=N-, -N=CH-, -CH=N-, -CH=N-N-, -CH=N-O-, -C=NNHCSNH-, -C=NNHCONH-, -CH=CH-, -CH(OH)-, -C(Cl)=C(Cl)-, -(CH₂)_n-, ethynylene, -N(R₅)-, -N(R₅₁)CO-, -N(R₅₂)SO₂-, -N(R₅₃)CON(R₅₄)-, -CON(R₅₅)-, -SO₂N(R₅₆)-, -O-, -S-, -SO-, -SO₂-, -CO-, oxadiazole-diyl, thiadiazole-diyl or tetrazole-diyl;

X₃ is alkyl, alkenyl, alkynyl, aryl, aralkyl, heterocyclic group, cycloalkyl, cycloalkenyl, thiazolylidenemethyl, thiazolidylidenemethyl, -CH=NR₆ or -N=C(R₇)R₈;

R₅, R₅₁, R₅₂, R₅₃, R₅₄, R₅₅ and R₅₆, each are hydrogen or alkyl;

R₆ is hydrogen, alkyl, hydroxy, alkoxy, carbamoyloxy, thiocarbamoyloxy, ureido or thioureido;

R₇ and R₈ each are independently alkyl, alkoxy or aryl; and n is 1 or 2;

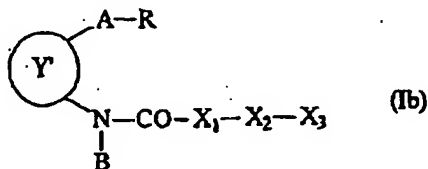
wherein a cyclic substituent may have one to three substituents selected from the group consisting of nitro, alkoxy, sulfamoyl, substituted- or unsubstituted-amino, acyl, acyloxy, hydroxy, halogen, alkyl, alkynyl, carboxy, alkoxy-carbonyl, aralkoxycarbonyl, aryloxy-carbonyl, mesyloxy, cyano, alkenyloxy, hydroxyalkyl, trifluoromethyl, alkylthio, -N=PPh₃, oxo, thioxo, hydroxyimino, alkoxyimino, phenyl and alkylenedioxy, or its salt or hydrate thereof; with the proviso that compounds (a) wherein X₁ and X₂ are a single bond, and X₃ is phenyl; and (b) wherein X₁ is a single bond, X₂ is -O-, and X₃ is benzyl are excluded.

9. Use of a PGD₂ antagonist comprising a compound of the formula (Ib) as defined in claim 8, or a salt or a hydrate thereof, as an active ingredient in the manufacture of a pharmaceutical composition for the treatment of diseases in which mast cell dysfunction is involved, tracheal contraction, asthma, allergic rhinitis, allergic conjunctivitis, urticaria, injury due to ischemic reperfusion, nasal occlusion and inflammation.

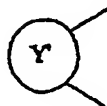
10. Use of a PGD₂ antagonist comprising a compound of the formula (Ib) as defined in claim 9, or a salt or a hydrate thereof, as an active ingredient in the manufacture of a pharmaceutical composition for the treatment of diseases in which mast cell dysfunction is involved, tracheal contraction, asthma, allergic rhinitis, allergic conjunctivitis, urticaria, injury due to ischemic reperfusion, nasal occlusion and inflammation.

Patentansprüche

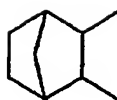
1. Verbindung der Formel (Ib):



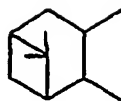
wobei



für



oder



steht,

wobei A Alkylen ist, das gegebenenfalls durch ein Heteroatom oder Phenylen unterbrochen sein kann, eine Oxo-
gruppe enthält und/oder eine ungesättigte Bindung aufweist;

B Wasserstoff, Alkyl, Aralkyl oder Acyl ist;

R für COOR_1 , CH_2OR_2 oder $\text{CON}(\text{R}_3)\text{R}_4$ steht;

R_1 Wasserstoff oder Alkyl ist;

R_2 Wasserstoff oder Alkyl ist;

R_3 und R_4 jeweils unabhängig Wasserstoff, Alkyl, Hydroxy oder Alkylsulfonyl sind;

X_1 eine Einfachbindung, Phenylen, Naphthylen, Thiophendiyl, Indoldiyl oder Oxazoldiyl ist;

X_2 eine Einfachbindung, $-\text{N}=\text{N}-$, $-\text{N}=\text{CH}-$, $-\text{CH}=\text{N}-$, $-\text{CH}=\text{N}-\text{N}-$, $-\text{CH}=\text{N}-\text{O}-$, $-\text{C}=\text{NNHCSNH}-$, $-\text{C}=\text{NNHCONH}-$,
 $-\text{CH}=\text{CH}-$, $-\text{CH}(\text{OH})-$, $-\text{C}(\text{Cl})=\text{C}(\text{Cl})-$, $-(\text{CH}_2)_n-$, Ethinylen, $-\text{N}(\text{R}_5)-$, $-\text{N}(\text{R}_{51})\text{CO}-$, $-\text{N}(\text{R}_{52})\text{SO}_2-$, $-\text{N}(\text{R}_{53})\text{CON}(\text{R}_{54})-$,
 $-\text{CON}(\text{R}_{55})-\text{SO}_2\text{N}(\text{R}_{56})-$, $-\text{O}-$, $-\text{S}-$, $-\text{SO}-$, $-\text{SO}_2-$, $-\text{CO}-$, Oxadiazoldiyl, Thiadiazoldiyl oder Tetrazoldiyl ist;

X_3 Alkyl, Alkenyl, Alkynyl, Aryl, Aralkyl, ein heterocyclischer Rest, Cycloalkyl, Cycloalkenyl, Thiazolinyldenme-
thyl, Thiazolidinyldenmethyl, $-\text{CH}=\text{NR}_6$ oder $-\text{N}=\text{C}(\text{R}_7)\text{R}_8$ ist;

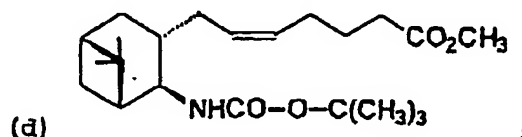
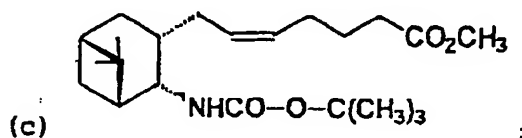
R_5 , R_{51} , R_{52} , R_{53} , R_{54} , R_{55} und R_{56} jeweils Wasserstoff oder Alkyl sind;

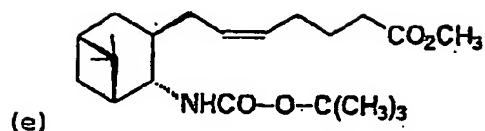
R_6 Wasserstoff, Alkyl, Hydroxy, Alkoxy, Carbamoyloxy, Thiocarbamoyloxy, Ureido oder Thioureido ist;

R_7 und R_8 jeweils unabhängig Alkyl, Alkoxy oder Aryl sind;

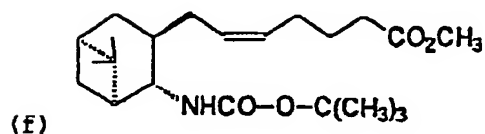
und n gleich 1 oder 2 ist;

wobei ein cyclischer Substituent 1 bis 3 Substituenten, ausgewählt aus Nitro, Alkoxy, Sulfamoyl, substituiertem oder
unsubstituiertem Amino, Acyl, Acyloxy, Hydroxy, Halogen, Alkyl, Alkynyl, Carboxy, Alkoxy-carbonyl, Aralkoxy-carbo-
nyl, Aryloxy-carbonyl, Mesyloxy, Cyano, Alkenyloxy, Hydroxyalkyl, Trifluormethyl, Alkylthio, $-\text{N}=\text{PPh}_3$, Oxo, Thioxo,
Hydroxyimino, Alkoxyimino, Phenyl und Alkylendioxy oder deren Salzen oder Hydraten davon, aufweisen kann; mit
der Maßgabe, dass die Verbindungen (a), wobei X_1 und X_2 Einfachbindungen sind und X_3 Phenyl ist; (b), wobei
 X_1 eine Einfachbindung ist, X_2 für $-\text{O}-$ steht und X_3 Benzyl ist;



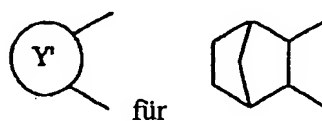


und



ausgenommen sind.

2. Verbindung nach Anspruch 1, ein Salz oder Hydrat davon, wobei

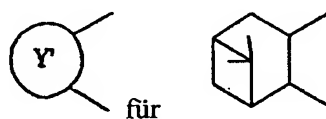


steht.

3. Verbindung nach Anspruch 2, ein Salz oder Hydrat davon, wobei R für COOR₁ steht.

4. Verbindung nach Anspruch 2, ein Salz oder Hydrat davon, wobei X₁ Phenylen oder Thiophendiyl ist, X₂ eine Einfachbindung, -N=N-, -CH=CH-, Ethinylen, -O-, -S-, -CO-, -CON(R₅₅)-, -N(R₅₁)CO- ist und X₃ Phenyl oder Thienyl ist.

5. Verbindung nach Anspruch 1, ein Salz oder Hydrat davon, wobei

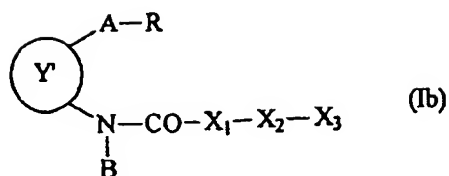


steht.

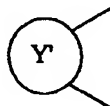
6. Verbindung nach Anspruch 5, ein Salz oder Hydrat davon, wobei B Wasserstoff ist, X₁ und X₂ beide eine Einfachbindung sind, X₃ Thienyl, Thiazolyl, Thiadiazolyl, Isothiazolyl, Pyrrolyl, Pyridyl, Benzofuryl, Benzimidazolyl, Benzothienyl, Dibenzofuryl, Dibenzothienyl, Chinolyl oder Indolyl ist.

7. Verbindung nach Anspruch 5, ein Salz oder Hydrat davon, wobei X₁ Phenylen, Thiophendiyl, Indoldiyl oder Oxazoldiyl ist, X₂ eine Einfachbindung, -N=N-, -CH=CH-, Ethinylen, -S- oder -O- ist und X₃ Aryl oder ein heterocyclischer Rest ist.

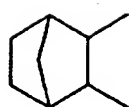
8. Verbindung der nachstehenden Formel (Ib), zur Verwendung in einem Verfahren zur Behandlung von Krankheiten, die eine Fehlfunktion der Mastzellen einschließen, trachealer Kontraktion, Asthma, allergischer Rhinitis, allergischer Konjunktivitis, Urtikaria, Verletzungen aufgrund von Ischämie-Reperfusion, Nasenokklusion und Entzündung:



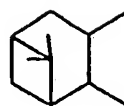
10 wobei



für



oder



steht;

wobei A Alkylen ist, das gegebenenfalls durch ein Heteroatom oder Phenylen unterbrochen sein kann, eine Oxo-
gruppe enthält und/oder eine ungesättigte Bindung aufweist;

30 B Wasserstoff, Alkyl, Aralkyl oder Acyl ist;

R für COOR₁, CH₂OR₂ oder CON(R₃)R₄ steht;

R₁ Wasserstoff oder Alkyl ist;

R₂ Wasserstoff oder Alkyl ist;

35 R₃ und R₄ jeweils unabhängig Wasserstoff, Alkyl, Hydroxy oder Alkylsulfonyl sind;

X₁ eine Einfachbindung, Phenylen, Naphthylen, Thiophendiyl, Indoldiyl oder Oxazoldiyl ist;

X₂ eine Einfachbindung, -N=N-, -N=CH-, -CH=N-, -CH=N-N-, -CH=N-O-, -C=NNHCSNH-, -C=NNHCONH-,
-CH=CH-, -CH(OH)-, -C(Cl)=C(Cl)-, -(CH₂)_n-, Ethinylen, -N(R₅)-, -N(R₅₁)CO-, -N(R₅₂)SO₂-, -N(R₅₃)CON(R₅₄)-,
-CON(R₅₅)-, -SO₂N(R₅₆)-, -O-, -S-, -SO-, -SO₂-, -CO-, Oxadiazoldiyl, Thiadiazoldiyl oder Tetrazoldiyl ist;

40 X₃ Alkyl, Alkenyl, Alkynyl, Aryl, Aralkyl, ein heterocyclischer Rest, Cycloalkyl, Cycloalkenyl, Thiazolinyldenme-
thyl, Thiazolidinyldenmethyl, -CH=NR₆ oder -N=C(R₇)R₈ ist;

R₅, R₅₁, R₅₂, R₅₃, R₅₄, R₅₅ und R₅₆ jeweils Wasserstoff oder Alkyl sind;

R₆ Wasserstoff, Alkyl, Hydroxy, Alkoxy, Carbamoyloxy, Thiocarbamoyloxy, Ureido oder Thioureido ist;

R₇ und R₈ jeweils unabhängig Alkyl, Alkoxy oder Aryl sind;

45 und n gleich 1 oder 2 ist;

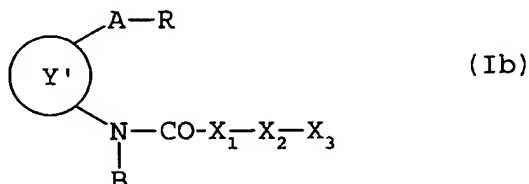
wobei ein cyclischer Substituent 1 bis 3 Substituenten, ausgewählt aus Nitro, Alkoxy, Sulfamoyl, substituiertem oder
unsubstituiertem Amino, Acyl, Acyloxy, Hydroxy, Halogen, Alkyl, Alkynyl, Carboxy, Alkoxycarbonyl, Aralkoxycarbo-
nyl, Aryloxycarbonyl, Mesyloxy, Cyano, Alkenyloxy, Hydroxyalkyl, Trifluormethyl, Alkylthio, -N=PPh₃, Oxo, Thioxo,
50 Hydroxyimino, Alkoxyimino, Phenyl und Alkylendioxy oder deren Salzen oder Hydraten davon, aufweisen kann; mit
der Maßgabe, dass die Verbindungen (a), wobei X₁ und X₂ Einfachbindungen sind und X₃ Phenyl ist; und (b), wobei
X₁ eine Einfachbindung ist, X₂ für -O- steht und X₃ Benzyl ist, ausgenommen sind.

9. Verwendung eines PGD₂-Antagonisten, umfassend eine Verbindung der Formel (Ib) wie in Anspruch 8 definiert
55 oder ein Salz oder Hydrat davon als wirksamen Bestandteil bei der Herstellung eines Arzneimittels zur Behandlung
von Krankheiten, die eine Fehlfunktion der Mastzellen einschließen, trachealer Kontraktion, Asthma, allergischer
Rhinitis, allergischer Konjunktivitis, Urtikaria, Verletzungen aufgrund von Ischämie-Reperfusion, Nasenokklusion
und Entzündung.

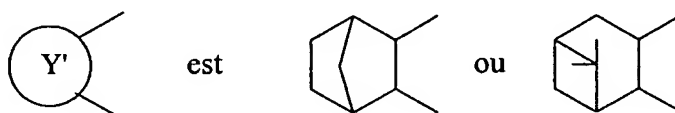
10. Utilisation d'un PGD_2 -Antagoniste, comprenant une Verbindung der Formel (Ib) wie in Anspruch 9 definiert oder ein Salz oder Hydrat davon als wirksamen Bestandteil bei der Herstellung eines Arzneimittels zur Behandlung von Krankheiten, die eine Fehlfunktion der Mastzellen einschließen, trachealer Kontraktion, Asthma, allergischer Rhinitis, allergischer Konjunktivitis, Urtikaria, Verletzungen aufgrund von Ischämie-Reperfusion, Nasenokklusion und Entzündung.

Revendications

1. Composé de formule (Ib) :



dans laquelle



A est alkylène qui, le cas échéant, est interrompu par (au moins) un hétéroatome ou phénylène, contient un groupe oxo, et/ou a (au moins) une liaison insaturée ;

B est hydrogène, alkyle, aralkyle ou acyle ;

R est COOR_1 , CH_2OR_2 ou $\text{CON}(\text{R}_3)\text{R}_4$;

R_1 est hydrogène ou alkyle ;

R_2 est hydrogène ou alkyle ;

R_3 et R_4 représentent chacun indépendamment hydrogène, alkyle, hydroxy ou alkylsulfonyl ;

X_1 est une simple liaison, phénylène, naphtylène, thiophènediyle, indolediyle, ou axazolediyle ;

X_2 est une simple liaison, $-\text{N}=\text{N}-$, $-\text{N}=\text{CH}-$, $-\text{CH}=\text{N}-$, $-\text{CH}=\text{N}-\text{N}-$, $-\text{CH}=\text{N}-\text{O}-$, $-\text{C}=\text{NNHCSNH}-$, $-\text{C}=\text{NNHCONH}-$, $-\text{CH}=\text{CH}-$, $-\text{CH}(\text{OH})-$, $-\text{C}(\text{C}1)=\text{C}(\text{C}1)-$, $-(\text{CH}_2)_n-$, éthynylène, $-\text{N}(\text{R}_5)-$, $-\text{N}(\text{R}_{51})\text{CO}-$, $-\text{N}(\text{R}_{52})\text{SO}_2-$, $-\text{N}(\text{R}_{53})\text{CON}(\text{R}_{54})-$, $-\text{CON}(\text{R}_{55})-$, $-\text{SO}_2\text{N}(\text{R}_{56})-$, $-\text{O}-$, $-\text{S}-$, $-\text{SO}-$, $-\text{SO}_2-$, $-\text{CO}-$, oxadiazolediyle, thiadiazolediyle ou tétrazolediyle ;

X_3 est alkyle, alkényle, alkynyle, aryle, aralkyle, groupe hétérocyclique, cycloalkyle, cycloalkényle, thiazolinyliidéneméthyle, thiazolidinyliidéneméthyle, $-\text{CH}=\text{NR}_6$, ou $-\text{N}=\text{C}(\text{R}_7)\text{R}_8$;

R_5 , R_{51} , R_{52} , R_{53} , R_{54} , R_{55} et R_{56} sont chacun hydrogène ou alkyle ;

R_6 est hydrogène, alkyle, hydroxy, alkoxy, carbamoyloxy, thiocarbamoyloxy, uréido ou thiouréido ;

R_7 et R_8 sont indépendamment chacun alkyle, alkoxy ou aryle ; et

n est 1 ou 2 ;

un substituant cyclique pouvant avoir de 1 à 3 substituants choisis parmi l'ensemble constitué par les nitro, alkoxy, sulfamoyl, amino substitué ou non substitué, acyle, acyloxy, hydroxy, halogéno, alkyle, alkynyle, carboxy, alkoxycarbonyl, aralkoxycarbonyl, aryloxycarbonyl, mésoxy, cyano, alkényloxy, hydroxyalkyle, trifluorométhyle, alkylthio, $-\text{N}=\text{PPh}_3$, oxo, thioxo, hydroxyimino, alkoxyimino, phényle et alkylènedioxy ;

ou ses sels ou ses hydrates ;

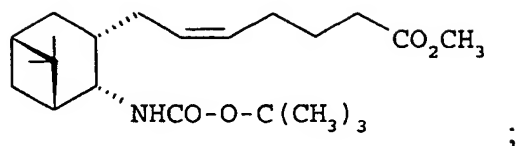
avec la condition que les composés

(a) dans lesquels X_1 et X_2 sont une simple liaison, et X_3 est phényle ;

(b) dans lesquels X_1 est une simple liaison, X_2 est $-\text{O}-$, et X_3 est benzyle ;

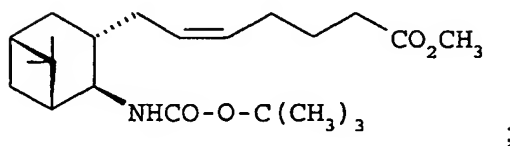
(c)

5



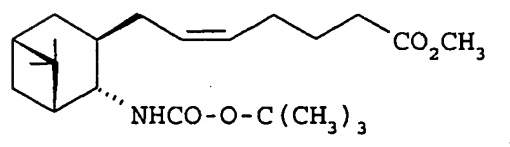
(d)

10



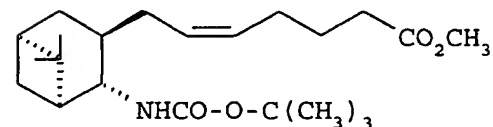
(e)

20



et
(f)

30



35

sont exclus.

40

2. Composé suivant la revendication 1, ses sels ou hydrates, où

45



3. Composé suivant la revendication 2, ses sels ou hydrates, où R est COOR₁.

50

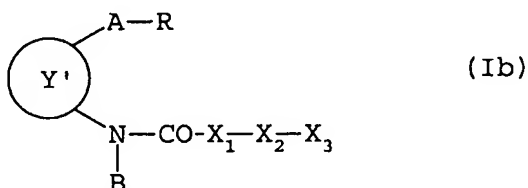
4. Composé suivant la revendication 2, ses sels ou hydrates, où X₁ est phénylène ou thiophènediyle, X₂ est une simple liaison, -N=N-, -CH=CH-, éthynylène, -O-, -S-, -CO-, -CON(R₅₅)-, -N(R₅₁)CO-, et X₃ est phényle ou thiényle.

5. Composé suivant la revendication 1, ses sels ou hydrates, où

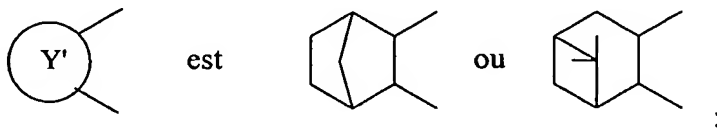
55



6. Composé suivant la revendication 5, ses sels ou hydrates, où B est hydrogène, X_1 et X_2 représentent chacun une simple liaison, et X_3 est thiényl, thiazolyle, thiadiazolyle, isothiazolyle, pyrrolyl, pyridyle, benzofuryl, benzimidazolyle, benzothiényl, dibenzofuryl, dibenzothiényl, quinolyle ou indolyle.
7. Composé suivant la revendication 5, ses sels ou hydrates, où X_1 est phénylène, thiophènediyle, indolediyle ou oxazolediyle, X_2 une simple liaison, $-N=N-$, $-CH=CH-$, éthynylène, $-S-$ ou $-O-$, et X_3 est aryle ou un groupe hétérocyclique.
8. Composé de formule (Ib) ci-après, pour utilisation dans le traitement de maladies impliquant un dysfonctionnement mastocytaire, la contraction trachéale, l'asthme, la rhinite allergique, la conjonctivite allergique, l'urticaire, le trouble dû à la reperfusion ischémique, l'occlusion nasale et l'inflammation :



dans laquelle



A est alkylène qui, le cas échéant, est interrompu par (au moins) un hétéroatome ou phénylène, contient un groupe oxo, et/ou a (au moins) une liaison insaturée ;

B est hydrogène, alkyle, aralkyle ou acyle ;

R est $COOR_1$, CH_2OR_2 ou $CON(R_3)R_4$;

R_1 est hydrogène ou alkyle ;

R_2 est hydrogène ou alkyle ;

R_3 et R_4 représentent indépendamment chacun hydrogène, alkyle, hydroxy ou alkylsulfonyl ;

X_1 est une simple liaison, phénylène, naphtylène, thiophènediyle, indolediyle, ou oxazolediyle ;

X_2 est une simple liaison, $-N=N-$, $-N=CH-$, $-CH=N-$, $-CH=N-N-$, $-CH=N-O-$, $-C=NNHCSNH-$, $-C=NNHCONH-$, $-CH=CH-$, $-CH(OH)-$, $-C(C1)=C(C1)-$, $-(CH_2)_n-$, éthynylène, $-N(R_5)-$, $-N(R_{51})CO-$, $-N(R_{52})SO_2-$, $-N(R_{53})CON(R_{54})-$, $-CON(R_{55})-$, $-SO_2N(R_{56})-$, $-O-$, $-S-$, $-SO-$, $-SO_2-$, $-CO-$, oxadiazolediyle, thiadiazolediyle ou tétrazolediyle ;

X_3 est alkyle, alkényle, alkynyle, aryle, aralkyle, groupe hétérocyclique, cycloalkyle, cycloalkényle, thiazolinyliidène, thiazolidinylidène, thiazolidinylidène, $-CH=NR_6$, ou $-N=C(R_7)R_8$;

R_5 , R_{51} , R_{52} , R_{53} , R_{54} , R_{55} et R_{56} sont chacun hydrogène ou alkyle ;

R_6 est hydrogène, alkyle, hydroxy, alkoxy, carbamoyloxy, thiocarbamoyloxy, uréido ou thiouréido ;

R_7 et R_8 représentent indépendamment chacun alkyle, alkoxy ou aryle ; et n est 1 ou 2 ;

un substituant cyclique pouvant avoir de 1 à 3 substituants choisis parmi l'ensemble constitué par les nitro, alkoxy, sulfamoyl, amino substitué ou non substitué, acyle, acyloxy, hydroxy, halogéno, alkyle, alkynyle, carboxy, alkoxy-carbonyl, aralkoxycarbonyl, aryloxy-carbonyl, mésoxy, cyano, alkényloxy, hydroxyalkyle, trifluorométhyle, alk-

ylthio, -N=PPh₃, oxo, thioxo, hydroxyimino, alkoxyimino, phényle et alkylènedioxy ;
ou ses sels ou ses hydrates ;
avec la condition que les composés

- 5 (a) dans lesquels X₁ et X₂ sont une simple liaison, et X₃ est phényle ; et
(b) dans lesquels X₁ est une simple liaison, X₂ est -O-, et X₃ est benzyle sont exclus.
9. Utilisation d'un antagoniste de PGD₂ comprenant un composé de formule (Ib) tel que défini dans la revendication
8, l'un de ses sels ou hydrates, en tant qu'ingrédient actif dans la préparation d'une composition pharmaceutique
10 pour le traitement de maladies impliquant un dysfonctionnement mastocytaire, la contraction trachéale, l'asthme, la
rhinite allergique, la conjonctivite allergique, l'urticaire, le trouble dû à la reperfusion ischémique, l'occlusion nasale
et l'inflammation.
10. Utilisation d'un antagoniste de PGD₂ comprenant un composé de formule (Ib) tel que défini dans la revendication
15 9, l'un de ses sels ou hydrates, en tant qu'ingrédient actif dans la préparation d'une composition pharmaceutique
pour le traitement de maladies impliquant un dysfonctionnement mastocytaire, la contraction trachéale, l'asthme, la
rhinite allergique, la conjonctivite allergique, l'urticaire, le trouble dû à la reperfusion ischémique, l'occlusion nasale
et l'inflammation.